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Title: The OPTiMiSE trial: a three-phase, double blind randomised switching study in first episode schizophrenia and schizophreniform disorder comparing amisulpride and olanzapine followed by open treatment with clozapine.

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Abstract: Background
It is not known whether switching antipsychotics or early use of clozapine improves outcome in (first-episode) schizophrenia.

Methods
The study was conducted in 27 centres in 14 European countries and Israel consisting of general hospitals and psychiatric specialty clinics. (Clinicaltrials.gov identifier is NCT01248195). Patients with schizophrenia or schizophreniform disorder were treated for four weeks with up to 800 mg/day amisulpride in an open design. Patients who did not meet symptomatic remission criteria at four weeks were randomized to continue amisulpride or switch to olanzapine (max 20 mg/day) during a six-week double blind phase. Patients who were not in remission at ten weeks were given clozapine (max 900 mg/day) for an additional 12 weeks in an open design. Data were analyzed using a generalised linear mixed model, with a logistic link and binomial error distribution.

Findings
Participants were recruited between May 26, 2011 and May 15, 2016 with 481 signing informed consent. Of the 446 patients in the ITT sample, 371 (83.2%) completed open amisulpride treatment, of whom 250 (67.4%) were in remission. 93 of the patients who were not in remission continued to the six-week double-blind switching trial with 72 patients (77.4%) completing

it (39 on olanzapine and 33 on amisulpride); 15 (45.5%) of the patients taking amisulpride reached remission versus 17 (43.6%) on olanzapine (p=.87). Of the 40 patients who were not in remission after 10 weeks of treatment, 28 (70.0%) were started on clozapine; 18 patients (64.3%) completed the 12-week treatment, of whom five (27.8%) met remission criteria.

Interpretation
In the large majority of patients in the early stages of schizophrenia, symptomatic remission can be achieved using a simple treatment algorithm comprising the sequential administration of amisulpride and clozapine.

Funding
European Commission; 7th Program (HEALTH-F2-2010-242114).

Comments from the editor

1) Please ensure the NCT number you have provided is correct (the one cited is only for the part of the study in Denmark).

The correct NCT number is NCT01248195, this has been adjusted in the manuscript.

2) Please describe the whole study (as in the protocol); you may then state, and reference, that parts of the study have/will be published elsewhere (eg, imaging, biomarker, psychosocial).

The following information is now included in the Methods section of the manuscript:

"Blood was drawn at the beginning and end of each treatment phase in order to relate proteomics, immune parameters and genetics to treatment outcome. In addition, patients who had remitted were randomised to a specific psychosocial intervention versus treatment as usual to test the effect on adherence. The results from these studies are not yet available and will be reported separately. Finally, MRI and MRS assessments were conducted in a subsample of participants."

3) Discuss your protocol amendments in the protocol: what was changed and the dates for all changes need to be provided.

As there were six amendments over the years; an overview of dates and content is provided in the Appendix.

4) Your protocol states that the secondary outcome will be measured by GAF but PSP is stated in your manuscript. Can you explain this discrepancy in the text? Also, subjective wellbeing is measured and reported in the manuscript but is absent from the protocol. Can we please include this as an exploratory endpoint? Also please report on secondary data in the results section and provide data (in an appendix please, to include study medication discontinuation Kaplan Meier and all other secondary outcomes).

Although the initial plan was to measure social function through GAF, early in the project (before the first patient was enrolled) it was decided to use the PSP instead, as this is a more elaborate assessment of social functioning. The protocol was not corrected in this regard as an

oversight. GAF was never assessed within this study. Subjective wellbeing is measured using the Subjective Wellbeing under Neuroleptics (SWN), as described in the protocol. These data have not yet been analyzed and – in view of the fast-track procedure – it was decided not to include them here.

A Kaplan Meier curve of dropout over time has been added to the appendix.

The following text was added to the Methods section:
"To assess the proportion of dropouts over time, a Kaplan Meier curve was used. Follow-up time was defined as the number of weeks between the date of the baseline visit and the date of the last visits of a patient. Patients who did not progress to a next phase because they were in remission were censored."

5) Please include abdominal circumference and frequency and severity of adverse effects in your methods and results, if these were measured. Please include an Adverse events table with total events, and with events separated by study phase. Please report all adverse events and not just those deemed to be related to study medication, though you are welcome to indicate which ones were or were not deemed to be related according to your criteria.
The abdominal circumference as well as the frequency and severity of side effects have been added to the Methods section:
"Frequency and severity of adverse events were assessed at each visit. In addition, weight, abdominal circumference and height were measured (..)".
Data for abdominal circumference are reported in the Results section, tables 1 (start of each phase) and 4 (end of each phase). As there were a large variety of adverse events, the full listing (apart from the more relevant side effects as listed in the tables of the manuscript) has been added to the appendix.

6) Did you complete the 48 and 74 week follow-up as mentioned in your protocol? If so please

include, or explain in your methods why these were not completed

The two long-term follow up visits are now described in the Methods section:

"Patients who did not meet remission criteria after completion of phase III, returned for a follow-up visit 48 weeks after baseline (26 weeks after the final phase III visit), where PANSS was assessed and rehospitalisation data was collected. For all patients who started phase I, a follow-up visit at 74 weeks post-baseline was scheduled to assess symptom severity and the current clinical diagnosis, as well as to collect data on hospitalisation."

Data from these visits are now described in the Results section:

"48-week follow-up visit

For patients who did not meet remission criteria after completion of phase III, a follow-up visit was scheduled, 48 week post- baseline (26 weeks after the final phase III visit). Out of the 11 non-remitters at the end of phase III, 8 patients returned for this visit. The mean total PANSS score was 70.5 (SD 22.3, range 40-104). Three patients met remission criteria during this visit. None of the patients were rehospitalised since the end of phase III.

74-week follow-up visit

For all patients who entered phase I, a follow-up visit was scheduled 74 weeks post-baseline. This visit was conducted for 167 patients. The clinical diagnosis at that time point was established: 13 patients (7.8%) were diagnosed with schizophreniform disorder, 22 patients (13.2%) with schizoaffective disorder, 123 patients (73.7%) with schizophrenia and 9 patients (5.3%) received other diagnoses (e.g. psychosis NOS, bipolar disorder, unspecified non-organic psychosis). PANSS data was available for 140 patients; the mean total PANSS score was 50.2 (SD 15.0; range 30-105). 95 patients (56.9%) met remission criteria. Seventeen out of 140 patients (10.2%) were hospitalized at least once since the most recent study visit."

7) Please include contraceptive use in your inclusion/exclusion criteria, as in the protocol.

This has been added to the Methods section of the manuscript:

"Female patients of childbearing potential were required to use a proper method of contraception."

8) Missing data: how were these handled? Please add a sentence to your Statistical analysis section in the methods.

We added the following to the Methods Section:

"Missing values were not imputed, as the GLMM analysis incorporates all available measurements, assuming that patients with available measurements are representative for all patients, including the patients with missing values. For side effects, we assumed that missing values indicated absence of side effects."

9) Please provide a CONSORT checklist, and ensure that your manuscript has been completed according to the guidelines. You have done this on the most part, but we need a check for our records.

The CONSORT checklist is provided separately.

10) Please ensure that all numbers are provided with % and vice-versa throughout the text and tables.

This has been checked and adjusted where applicable.

11) Please provide p values to 4 decimal places, or 2 significant figures (ie, exact to p<0.0001).

This has been checked and adjusted where applicable.

12) The declaration of interest and acknowledgment section of the manuscript are missing (acknowledgments are optional!). Please provide author statements and ICMJE forms for all authors (forms can be found at https://urldefense.proofpoint.com/v2/url?u=http-3A__www.thelancet.com_for-2Dauthors_forms&d=DwICaQ&c=shNJtf5dKgNcPZ6Yh64b-A&r=7WxFffoccXhX-bfveeLq6q7B5wq2ACLrQYNkkiB8Fh8&m=3CIIAYKNUtsVTIFeJUADzYCAlI-FdLmD5of0q5psuwA&s=kjJIL-L3JtXnLIf33HKXaL5JtxQxs5hnNyFBtbjyph4&e=)

The required forms (author statements and ICMJE forms) for all authors have been submitted with the original submission to 'The Lancet'. In case these were not forwarded to 'The Lancet Psychiatry', we can provide them immediately. We apologize for the missing summary statements, they have been added to the current version of the manuscript.

13) Would it be possible to include information about study sites and participants who are not authors in the appendix?
An overview of the 'OPTiMiSE Study Group' authors and all participating centers is included in the appendix.

14) Would it be possible for you to provide editable versions of all figures to be included in the manuscript? Artwork guidelines (for what constitutes an editable file) can be found as a PDF at https://urldefense.proofpoint.com/v2/url?u=http-3A__www.thelancet.com_for-2Dauthors_forms&d=DwICaQ&c=shNJtf5dKgNcPZ6Yh64b-A&r=7WxFffoccXhX-bfveeLq6q7B5wq2ACLrQYNkkiB8Fh8&m=3CIIAYKNUtsVTIFeJUADzYCAlI-FdLmD5of0q5psuwA&s=kjJIL-L3JtXnLIf33HKXaL5JtxQxs5hnNyFBtbjyph4&e=.
We have created new versions in EPS format.

15) To enable readers to better appreciate research findings and to encourage full and transparent reporting of outcomes, The Lancet family journals offer to publish a webaddress in accepted paper that links to the study's protocol on the author's institutional website (see Lancet 2009; 373: 992). This is particularly encouraged for randomised controlled trials, but is welcome for all types of research.
A specific website for the project is available. Even though it is separate from the author's institutional website, we would appreciate it when this address could be published: www.optimisetrial.eu

16) Finally, we encourage authors to share any additional data, that would facilitate the replication or further analysis of their work—eg, the raw numbers underlying their analysis or

the code for any modelling. Mendeley Data is a secure online repository for research data, permitting archiving of any file type and assigning a permanent and unique digital object identifier (DOI) so that the files can be easily referenced. If authors wish to share their supporting data, and have not already made alternative arrangements, a Mendeley DOI can be referred to in a section entitled "Data sharing" at the end of the Methods section, ahead of "Role of the funding source". If authors have already deposited their data in another repository, or have made other arrangements for data to be shared (eg, by means of an adjudication process or contacting the authors), they should use this section to elaborate.
Although we are in favor of data sharing, the informed consent documents used for the current study do not allow for data sharing outside our project Consortium without additional consent from the participant.

Additional comment received per email on April 22 from the editor:
I just wanted to follow up with one more comment that needs addressing that I accidentally omitted from the initial email: your power calculations appear to be missing from the Methods section of your manuscript, and the fact that the Phase II part of your study did not reach power is concerning. You mention in your discussion that having a higher number of participants in this phase probably would not have changed the study conclusions (which may well be true); however, the reporting of your power calculations needs to be present and transparent. Would you also be able to add this to your revision?
The power calculation has been added to the Methods Section of the manuscript, "Power analysis and statistical analysis".

"Data of the EUFEST study (1) showed that about 40% of the patients on amisulpride were in symptomatic remission within four weeks. However, halfway through the study almost 60% of phase I patients met remission criteria. Subsequently, the power analysis was adjusted to the following: based on EUFEST we expect that 50% of the four-week non-responders who stay on amisulpride will be in symptomatic remission after another six weeks of treatment (10 weeks from treatment initiation). If the percentage of patients in remission increases from 50% to 70% as a result of switching to olanzapine (which is an estimation, as there are no prior studies on

this topic), the two treatment arms will have to contain 90 patients each to obtain a statistical power of .79 with a type-I error rate of .05. If we consider that the drop out rate is approximately 30% and the remission rate 60% (both observations after 250 patients had been enrolled into the study), than this implies that at least 487 patients will have to be included at baseline, taking into account a drop-out of 30% during phase II (observation in first 50 phase II patients)."

Reviewers' comments:

Reviewer #1: Comments to the author:

In my opinion this is an important study, but the authors failed to explain why in any detail.

We have added the following paragraph in the Introduction:

"Indeed, one of the most relevant questions in the treatment of the early phase of schizophrenia – and an essential ingredient in any treatment algorithm - is whether switching to another antipsychotic improves outcome when a patient has not responded to the treatment that was initiated."

1. The authors spent many words on the lead-in and the open-label extension but did not adequately present full details about Phase 2, the important part of the study. The emphasis should be on Phase 2 and some of the details in the lead-in could go in the web supplement.

We have added to the Introduction:

"Another aspect that has often been lacking in treatment studies in schizophrenia is a clinically relevant outcome measure. Generally, response to treatment has been defined as a reduction in the Positive and Negative Syndrome Scale (PANSS) total score of >20% but it has been argued that a more stringent outcome is 'remission', analogous to cancer treatment and reflecting an almost complete absence of the psychotic symptoms of schizophrenia.[3] This measure is clinically relevant and useful as an outcome in clinical trials.[4,5] "

We have added to the Results:

"Baseline characteristics of the 93 patients for the two treatment groups are depicted in Supplemental Table 1. There were no statistically significant differences in proportion or means between the two randomized groups, as expected."

"An extensive report of all side effects reported is provided in a table in the appendix."

2. I would recommend adding several tables that systematically report the critical statistics for both the intent-to-treat analysis and the observed case analysis of Phase 2, giving baseline mean standard deviations and sample size, with values for intermediate time points as well as the endpoint. Most studies test for baseline differences to see if randomization worked and baseline differences should be evaluated for the 92 patients who received medication in phase

Please see above. We have added Tables on Baseline characteristics and side-effects of Phase II. We added the following to the results section:

"Baseline characteristics of the 93 patients for the two treatment groups are depicted in Table 5. There were no statistically significant differences in proportion or means between the two randomized groups."

2. The authors failed to give the statistical methods in any detail for Phase 2, allowing only one sentence with only the statement: "a factor in the GLMM.". In any case we only know what the factor is. What we don't know is what the other variables are. Since the readers are psychiatrists, this doesn't mean much. I'm not questioning the statistics and I'm sure they were well done, but there should be enough detail in any methodology that a person could replicate the study using the same design. I have no problem
with the conservative estimate of number of responders at endpoint of any given phase. However, I think it would be appropriate to give full numerical statistics on the qualitative

response versus non-response at each time point for Phase 2 in a numerical table. It should also be clear what statistics were done for the continuous data as well as for the remission data.

The description of statistical methods has been extended with more details. We have also created a table (Table 5) with baseline characteristics in the two randomized groups of phase II. No statistical significant differences between the groups were found.

We added the following (additions are underlined):

Remission, as assessed at the final visit of each phase, was first summarized as counts and percentages. Subsequently, remission at each visit was analysed using a generalised linear mixed model (GLMM), with a logistic link and binomial error distribution. Variables included were visit number as a categorical variable and the baseline PANSS score as a continuous covariate. In this way, all visits contributed to the estimate of the between patient variance, thereby making the estimate of remission at the final visit more robust while accounting for dropout. For phase II a comparison was made between the amisulpride and olanzapine arm, by including the treatment arm as a factor in the GLMM. The cumulative proportion of patients in remission over all three study phases was calculated using the number of patients in remission at the last visit of each phase, i.e. the phase completers in remission. We used the conservative assumption that dropouts within a phase did not reach remission throughout the study. Patients eligible for a next study phase, but not continuing into that phase, were assumed not to be different from patients who did continue. To assess the proportion of dropouts over time, a Kaplan Meier curve was used. Follow-up time was defined as the number of weeks between the date of the baseline visit and the date of the last visits of a patient. Patients who did not progress to a next phase because they were in remission were censored. Side effects were summarized per visit and per phase and expressed as percentages. Missing values were not imputed, as the GLMM analysis incorporates all available measurements, assuming that patients with available measurements are representative for all patients, including the patients with missing values. For side effects, we assumed that missing values indicated absence of side effects. All quantitative scores, including the PANNS, were summarized as means and standard

deviation and differences between groups were assessed by a t-test. Dichotomous variables were expressed as counts and percentages and differences between groups were assessed by Chi square tests. Differences between groups in proportions were calculated and a 95%CI according to Wilson's method. In all analyses, the criterion for statistical significance was P < 0.05. SPSS version 25 was used for all analyses. A Data Safety Monitoring Board oversaw the study.

3. There were a number of instances in the paper where I could not get the numbers to add up. In the text the author mentioned that seven patients dropped out of the olanzapine arm, but in the consort diagram six are noted. It is important not to confuse patients randomization with not entered in the study with dropouts on drug. I also could not calculate some of the percentages in the text. Some of the numbers and percentages in text or in Table 4 or elsewhere didn't make sense. Side-effect data should reflect every patient exposed to the drug. I realize that some of these problems are trivial but they should be fixed in the revision.

We went through the manuscript and tables in detail to resolve the issues with inconsistencies in the numbers. Regarding the side effect data, we strongly prefer to report the presence of adverse events for those patients who have side effect data available for the applicable visit only. In case we would use the full sample of patients exposed to drug, we would assume that patients for whom side effect data is missing did not experience these particular effects, which may result in misleading numbers.

4. One could make more of the limitation of sample size of only a limited number of Phase 2 completers, but this is mitigated by the nonsignificant trend of olanzapine to do worse. If switching produced benefit. Olanzapine would've had to do better, for a positive results but it treaded to do worse and 92 is a reasonable N. I think that is a logical fallacy for any family of drugs where efficacy differences might potentially occur to conclude that because to drug with similar efficacy do not differ on switching, that switching from one drug low in efficacy to another drug high in efficacy might yield a better result. I do not think you can rule out the

possibility that those responding to Clozapine were true drug responders because you had no placebo or other comparator for this phase for the passage of time.

Indeed, we had indicated as such in the discussion:
"Third, it could be argued that a comparison between continuation with amisulpride and switching to clozapine in Phase III would have been of interest; the current design cannot address that question. Indeed, whether clozapine has an added benefit over continuation with amisulpride after ten weeks of its use needs further study."

5. It's been known for many years the first-episode patients have high remission rates. I do feel that the author adequately discussed the implication that Phase 1 is open. The discussion of reference #16 seems convoluted and the discussion of reference #17 might benefit from a change of word order, moving the last sentence up in the paragraph. There are various other studies using switching strategies, but I agree with the author's choice of just discussing these two studies. I think this is a fine study and there's something not quite right about saying that you are the first to study this question in first-episode patients and then stating the results of another previous study. I think this issue might be fixed by adding one word. Nevertheless, this paragraph is rather convoluted. I recognize that my criticisms are small except for the need for systematic tables of both observed-case and intent-to-treat and an explicit statement of methodology and I do think the paper could
benefit from a revision.

We have changed both paragraphs.
The first paragraph on reference 16 now reads:
"To our knowledge, this is the first study to examine the effects of switching antipsychotics in patients with (first-episode) schizophrenia who do not respond to their initial antipsychotic treatment (response has been defined differently in the various studies; we used remission in the current study). With the exception of one study, all previous studies were conducted in the later, chronic, stage of the illness. Moreover, the single study in first-episode schizophrenia did not

assess whether switching was more effective than staying on the original treatment (for review see[14)]).”

The paragraph on reference 17 now reads:
“The only double-blind study that compared switching versus continuation in non-responders was conducted in patients with chronic schizophrenia (age around 42 years). Response in the first two weeks was defined as ≥20% reduction in total PANSS scores. This corresponds to a lesser degree of clinical improvement than the symptomatic remission criterion used in the present study.[17] Patients who did not respond to a two-week open trial with risperidone (2-6 mg/day) were randomized to either continuing on risperidone or were switched to olanzapine (10-20 mg/day). Switching resulted in a small but significantly greater reduction in total PANSS scores after four weeks.”

It is a truly excellent study, clinically important, but not systematical written up.

Reviewer #2:
1. Composite outcomes, in which multiple endpoints are combined, are actually used as the primary outcome measures in this trial. Multiplicity adjustment is necessary.
The primary outcome is remission, a single binary variable. Only in phase II a comparison between randomized groups is made. Therefore, we do not consider this to be multiple endpoints.

2. On page 8, Missing Completely at Random (MCAR) is assumed in the statistical analysis. This is a strong assumption. More discussions on the missing data mechanism is necessary.
We have added details about missing values and the way the GLMM method deals with it in the Method section.
“Missing values were not imputed, as the GLMM analysis incorporates all available measurements, assuming that patients with available measurements are representative for all

patients, including the patients with missing values. For side effects, we assumed that missing values indicated absence of side effects."

3. For the key secondary endpoint, a large *p* value in a null hypothesis significance testing does not indicate the equivalence between olanzapine and amisulpride. A confidence interval is a good way to present this result. An equivalence test is an even better choice.
The difference in proportion with 95%CI has been added to the text.

4. It is not easy to distinguish the remission rate of olanzapine from that of amisulpride in Phase 2 in Figure 4 and 6. The ends of error bars may use different symbols for olanzapine and amisulpride.
We have created editable versions of the figures, and we suggest to leave this to a graphical artist of the journal.

Reviewer #3: This is the first study to investigate the efficacy of switching of antipsychotic among patients with first episode schizophrenia who do not respond to their first antipsychotic treatment. Therefore, it is enormously important study concerning clinical practice. I have a few comments:

1. The results show that remission can be reached among ¾ of patients by continuation of amisulpride (and in some cases switching to clozapine). However, I think that reaching remission is not the main issue in the treatment of schizophrenia, but STAYING in remission is the essential goal. I think that this should be dealt in the Discussion.

We have added the following to the discussion:
"Finally, although our results show that a large majority of first-episode schizophrenia patients reaches remission within a few months of treatment, failing to stay in remission remains a major impediment in the treatment of schizophrenia [(22).]"

2. Cohort studies show that about half of the first-episode patients do not go to pharmacy to pick-up any antipsychotic treatment after their first hospital discharge. This indicates that in real-life setting, compliance/adherence to use oral medication is rather low and use of LAIs might partially overcome this problem.
We did not specifically mention the use of LAIs in this study (since it is outside its scope) although we did address, as suggested by this reviewer (see above), the issue of failing to stay in remission (which has many causes).

3. Minor issues: In the abstract, "Interpretation" does not answer to "Background" question. ("It is not known whether switching antipsychotics or early use of clozapine improves outcome in (first-episode) schizophrenia"). I think that the text in the "Interpretation" should be replaced by text from "Research in context" paragraph ("The results suggest that in the large majority of patients in the early stages of schizophrenia, symptomatic remission can be achieved using a simple treatment algorithm comprising the sequential administration of amisulpride and clozapine.").

We have followed the suggestion by this reviewer and used the text from the Research In Context "Implications" for the "Interpretation" in the abstract. The Interpretation section of the abstract therefore now reads:
"In the large majority of patients in the early stages of schizophrenia, symptomatic remission can be achieved using a simple treatment algorithm comprising the sequential administration of amisulpride and clozapine."

4. In the Abstract, it is stated "… 18 patients completed the 12-week treatment, of whom five (17.9%) met remission criteria". 5 of 18 is 27.8%. (It seems that 17.9% refers to ITT, i.e., 5 of 28.)
Thank you for pointing this out, the applicable text has been adjusted as follows: '18 patients (64.3%) completed the 12-week treatment, of whom five (27.8%) met remission criteria.'

Reviewer #4: THELANCETPSYCH-D-18-00228

This is an important study that investigates the value of switching antipsychotic agents for individuals with a first episode of schizophrenia and schizoaffective disorder who have not remitted with their first trial of antipsychotic medication. The results of the study are clear but the appropriate interpretation is less clear cut due to limitations in the study design. It would be valuable for the authors to address the following issues:

1. While the choice of amisulpiride over olanzapine as a first line antipsychotic is justifiable, it would be valuable to be more clear about their rational for considering amisulpiride to be the less toxic alternative. The current wording is overly simplistic. This would provide the authors with opportunity of articulating the relative risks of these two medications. Olanzapine carried a greater risk of weight gain and metabolic complications including diabetes while current evidence suggest that amisulpiride is thought to be associated with greater QTc prolongation and a tardive dyskinesia risk that is greater by a modest degree compared to olanzapine though substantially lower than the risk associated with first generation antipsychotics.

We have changed the text as follows.

"Although both drugs have multiple side-effects, in the case of amisulpride these are mostly limited to extrapyramidal symptoms and hyperprolactinaemia (although QTc prolongation can occur at higher doses), while those associated with olanzapine increase the risk of cardiovascular complications - and are therefore more serious in the long term than those associated with amisulpride[6]. It would therefore make sense to initiate treatment with amisulpride."

2. It is incorrect to state that in clinical practice the interval between the onset of treatment and the initiation of clozapine is 10-12 years. My understanding is that more recent studies have reported somewhat shorter delays. Perhaps this could be worded as "as long as 10-12 years".

The applicable text in the Introduction has been adjusted to reflect the reviewer's comment:

However, in clinical practice the interval between the onset of treatment and the initiation of clozapine is as long as 10-12 years.[10]

3. Two objectives of the study are described. The first objective is clear but the second objective less so. It seems very straightforward that a simple treatment algorithm would facilitate earlier treatment with clozapine. The question is really whether earlier treatment with clozapine leads to improvement in patients who have not remitted after 10 weeks of antipsychotic treatment. Rewording of the second objective would be valuable.

We have changed the wording of the second objective as follows:
"Can earlier treatment with clozapine improve outcome in patients who have not remitted after 10 weeks of antipsychotic treatment?"

4. The title of the paper states that this is a study of first episode schizophrenia and schizoaffective disorder but the Methods section also includes schizoaffective disorder. It may be better to just use the term "schizophrenia", "schizophrenia spectrum disorders" or "non-affective psychoses" in the title.

Although this is correct, we refrained from changing the title in this respect. The proportion of schizoaffective patients in this study was quite small (6%) and adding this group to the title would have made it overly long.

5. "Patients were required to provide written informed consent." This is poorly worded as it could be interpreted to mean that patients were not given a choice. "All study participants provided written informed consent" would be more accurate.
The applicable text in the Methods has been adjusted to reflect the reviewer's comment: 'All study participants provided written informed consent.'

6. Individuals were excluded if they had psychotic symptoms that interfered with their functioning for over two years. It is not clear why this exclusion was used. It likely impacted substantially on their results as there is evidence that those with more insidious onset and longer DUP are less responsive. The rationale for this exclusion criteria and its likely impact on the study results should be discussed in the Discussion.

Thank you for pointing this out. The applicable text in the Methods section has been adjusted in line with the text in the study protocol: 'Patients were excluded if the time interval between the onset of psychosis and study entry exceeded two years.'

7. The most controversial aspect of the study is likely to be the decision to limit the initial trial of amisulpiride to 4 weeks. Previous research (Samara et al 2015) has reported that patients with schizophrenia who have not experienced minimal improvement after two weeks on a given antipsychotic are unlike to improve with that agent. That is very different from what was done in the current study, i.e. switching at 4 weeks if criteria for remission were not met. It is not surprising that many patients who stayed on amisulpiride continued to improve to the point that they met remission criteria after 10 weeks of treatment.

Many authors would argue that 4 weeks is more than adequate to address non-response, as this reviewer also suggests by quoting Samara et al, 2015, where it is concluded that 2 weeks is adequate to make the decision whether or not the patient has responded to treatment. In fact, to quote from that paper: "…. the assessment of final nonresponse at week 4 was associated with higher specificity of the diagnostic test than was assessment of nonresponse at week 6 or later." This does suggest that 4 weeks is in fact sufficient for an initial trial.

We have added to the Discussion:

"Fourth, it may be argued that a 4-week trial is not sufficiently long to decide whether to switch or not. However, a recent meta-analysis suggests this period is sufficient [(22)]."

This is important because those patients randomized to olanzapine should not be considered to have been amisulpiride non-responders. In the seminal study of clozapine versus chlorpromazine (CPZ) for first episode schizophrenia (Lieberman et al. 2003), clozapine was not found to be superior to CPZ. Because the response rate to first line antipsychotics is so high, it was not possible to demonstrate additional benefit from chlorpromazine. Subsequent studies of first episode non-responders have shown clozapine to be more effective. The current study is also limited by a similar issue. It is possible that olanzapine is more effective for first episode patients who have not responded to amisulpiride. The current study did not really test this as many of the patients in Phase II of the study were not amisulpiride non-responders. As a result, it would be reasonable to conclude that patients who have not remitted after four weeks of amisulpiride treatment do not benefit from switching to olanzapine. However, this might not be the case if patients had been given a longer trial (e.g. 12 weeks) to more definitively establish poor response to amisulpiride.

It is important to point out here that we studied <u>remission</u>, not just response. The reviewer is right that some of the patients who continued into Phase II may have been 'responders' depending on the criteria used in some of the studies the reviewer is referring to. However, as we have now added to the Introduction, one of the unique characteristics of the current study is that we defined outcome as the more clinically relevant (and stringent) outcome, remission. Also, as argued by the reviewer, there is no convincing evidence that longer treatment would improve chances of remission (except for clozapine).

8. It is of note that the dropout rate was not significantly different for olanzapine versus amisulpiride in this study. Given that a number of previous studies including the CATIE study have found that olanzapine has been associated with lower dropout rates (though not compared to amisulpiride), it is striking that the dropout rate was twice as high in the amisulpiride group. One certainly wonders whether the lack of statistical significance is best explained by low statistical power. It would be worth reporting the effect size and comparing it to effect sizes for discontinuation rates seen after four weeks of treatment in the CATIE study

and the 2003 Lieberman et al study comparing olanzapine and haloperidol in first episode schizophrenia.

We have now added the confidence intervals of the drop our rates in Phase II:

"Dropout rates between the two treatment arms did not differ significantly, although there was a trend in favor of olanzapine; 29.8% of patients randomized to amisulpride dropped out (n=14) versus 15.2 % (n=7) on olanzapine, a difference of 14.5%, 95%CI -2.5% to 30.7% (p=.093)."

9. Given the brevity of the Phase I trial of amisulpiride, the requirement that remission criteria not be met to enter Phase II, and the substantially lower dropout rate seen with olanzapine, the question of whether there might be value in having a trial with olanzapine for those who fail to remit after a full trial of asenapine has not addressed in this study.

We assume the reviewer means amisulpride (not asenapine). As indicated above, we do not consider a 4-week trial insufficient to achieve remission. To wit, 56% of patients reached remission during those weeks, more than was initially assumed on the basis of prior data. It is unclear what the reviewer considers a full trial.

10. A variety of clinical scales were used including the SWN, CDSS, and PSP. However, no data is provided for these measures or their change during the different phases of the study.

As indicated in our response to the editor, these data are not yet available.

11. Rates of EPS and sexual side effects during open label amisulpiride treatment were very high. The 2013 metaanalysis by Leucht et al. in Lancet also found amisulpiride to have amongst the largest effects on QTc. Does this not raise questions about whether amisulpiride should be considered as the ideal first line treatment for a first episode of schizophrenia?

We never make the claim in our paper that amisulpride is the 'ideal' first line treatment for schizophrenia. We chose the drug on the basis of the efficacy and side-effect data from the Eufest trial.

12. Twelve patients decided not to continue into the 12-week open label Phase III for various reasons and 10 dropped out during Phase 3. It would be important to know whether these individuals were followed and how their improvement compared with those who were treated with clozapine.
None of the phase II non-remitters who decided not to continue into phase III, attended the 74 week post-baseline follow-up visit, so no information is available on their illness progression. Only two of the phase III drop outs attended the 74 week visit, both were not meeting remission criteria at the time. As this data is very scarce and therefore not very informative, we chose not to include this in the manuscript.

13. Those treated with clozapine showed a mean improvement of 18.4 points relative to their phase III baseline. However, the change in PANSS shown in Figure 6 for those treated with clozapine appears to be much smaller. Figure 6 should be reviewed for accuracy.
The reason for the difference is that 18.4 points is the difference with baseline within patients who completed phase III, while in Figure 6, the data per visit are used: at the baseline, more patients have data, than the ones completing phase III.

14. "Extrapolating, these data suggest that if a patient fails to achieve remission on their first antipsychotic drug, switching to a different drug is no more effective than remaining on the same medication and waiting to see if remission is achieved at a later stage." This conclusion is not supported by the results of the study and should be revised.

This is indeed true. That is why we stated in the discussion:

“Although these results need to be replicated and broadened (using different antipsychotics)…….”

The study is remarkable in demonstrating that, using a structured algorithm for treating a first episode of schizophrenia, over 75% of patients met criteria for remission within 22 weeks. There was no advantage to switching from amisulpiride to olanzapine after four weeks if remission had not been achieved. It is not possible to generalize this finding to other antipsychotics as amisulpiride and olanzapine were selected due to their comparable and superior effectiveness compared to other second generation antipsychotics (SGA) in clinical trials and recent meta-analyses. It is not correct to assume that the study results would have been the same if another SGA such as risperidone or aripiprazole were to replace amisulpiride as the first medication used in the algorithm.

Again, we refer to our response above. We do realize that these results cannot simply be broadened to all antipsychotics. That is why we stated in the discussion:
“Although these results need to be replicated and broadened (using different antipsychotics)…….”

In countries where amisulpiride is available, this may be of little consequence since it can be argued that amisulpiride should be the first drug tried in the treatment algorithm. It becomes relevant if amisulpiride cannot be tolerated by a patient. The implications of this study for the treatment of patients in North America, where amisulpiride is not available, are quite different. This should be discussed in the Discussion section.

We thought that commenting on the unavailability of amisulpride in the USA and its consequences would be belaboring the obvious. We therefore refrained from doing so.

This study in no way addressed the issue of whether switching to olanzapine at 4 weeks or following a more extended period of a first line agent might be beneficial as I have explained

above. This is undoubtedly an important study but it is important that the study results be interpreted critically and accurately.

Many authors would argue that 4 weeks is more than adequate to address non-response, as this reviewer also suggests by quoting Samara et al, 2015, where it is concluded that 2 weeks is adequate to make the decision whether or not the patient has responded to treatment. In fact, to quote from that paper: "…. the assessment of final nonresponse at week 4 was associated with higher specificity of the diagnostic test than was assessment of nonresponse at week 6 or later." This does suggest that 4 weeks is in fact the right time for an initial trial.

We therefore feel that 4 weeks was adequate. We have therefore added the following sentence tot he discussion:

Fourth, it may be argued that a 4-week trial is not sufficiently long to decide whether to switch or not. However, a recent meta-analysis suggests this period is sufficient [(22)].

15. "this study is the first study to examine the effects of switching …in patients who do not respond to their first antipsychotic treatment". This is not accurate. Patients were included in Phase II if they failed to meet remission criteria after 4 weeks. This is not the same as response as clearly many of these patients were responding but not so rapidly that they met criteria for remission after only four weeks of treatment.

In our opinion this statement is correct since there have been no studies examining the effect of switching vs. continuation in first-episode schizophrenia. The fact that we defined non-response as failure to reach remission does not conflict with that statement. Nevertheless we changed the sentence to clarify this issue, as follows:
"To our knowledge, this is the first study to examine the effects of switching antipsychotics in patients with (first-episode) schizophrenia who do not respond to their initial antipsychotic

treatment (response has been defined differently in the various studies; we used remission in the current study).”

16. Reference 14 is not correct.

This is a review article; this may have been unclear. We have changed the sentence as follows:

“Moreover, the single study in first-episode schizophrenia did not assess whether switching was more effective than staying on the original treatment (for review see[14]).”

17. "…it may be feasible to define non-response on the basis of a single course of antipsychotic treatment." While this may be the case, the current study does not provide support for this for the reasons articulated in Points 7-9 above.

The reviewer is right that we should have used non-remission instead of non-response. We have therefore changed the sentence as follows:

"…it may be feasible to define non-response (operationalized as failure to achieve remission) on the basis of a single course of antipsychotic treatment."

18. No information was provided about rates of smoking. This is an issue for both dosing of olanzapine and clozapine as smoking induces cytochrome P450A12. This may have led to under-dosing of olanzapine which may have biased the results in favor of amisulpiride.

Smoking status was not assessed. However, as we reported, doses of olanzapine were actually numerically HIGHER in the non-remitters. Thus, under-dosing is an unlikely explanation of non-remission (as we had stated in the discussion).

"Critically, the doses in remitters and non-remitters were similar, with those in the non-remitters numerically higher in all phases for all drugs, suggesting that non-remission was not attributable to underdosing."

Reviewer #5: Please address the following:

The MS is rather poorly written, particularly in its persistent alternating of terms such as improvement, response and remission, when the trial examined only remission.

We have addressed this throughout the manuscript.

The definition of remission should be more explicit.

We could not have been more explicit than we were, stating in the Method section: Symptomatic remission was defined according to the criteria of Andreasen: eight specific symptoms rated by the PANSS (items P1, P2, P3, N1, N4, N6, G5 and G9) are at the most only mildly present (maximum rating of '3'), meaning that they do not interfere with daily life functioning.[15]

Many people not reaching 'remission' would have palpably improved. This is important in phase II - I suspect all of the amisulpride remitters in this phase were improvers in Phase I.

This may certainly be true. However, the main objective of this study was to adhere to a far more stringent outcome than just improvement –because it is considered clinically more relevant; that is why we chose to use remission as an outcome. To further clarify this, we added the following to the introduction:

"Another aspect that has often been lacking in treatment studies in schizophrenia is a clinically relevant outcome measure. Generally, response to treatment has been defined as a reduction in the Positive and Negative Syndrome Scale (PANSS) total score of >20% but it has been argued that a more stringent outcome is 'remission', analogous to cancer treatment and reflecting an almost complete absence of the psychotic symptoms of schizophrenia.[3] This measure is clinically relevant and useful as an outcome in clinical trials.[4,5]"

I do not agree that adverse effects were as expected: amisulpride seems much more 'atypical' than olanzapine in terms of movement disorders - a strange finding.

In fact, we proposed an explanation for this 'strange' finding. We stated:

In phase II, side effects were more prominent in the patients on olanzapine compared to amisulpride: this may have been because those intolerant to amisulpride had dropped out in the earlier phase or had developed tolerance.

Note spelling of akathisia.
'Akathesia' has been adjusted to 'akathisia' in the applicable table. The data have been checked and no errors were found.

The main finding is that switching to olanzapine is a waste of time. This is not mentioned in the abstract. It is a crucial finding.

This conclusion in our opinion (and that of reviewer 4) seems a bit too broad. Since we only tested olanzapine vs amisulpride in this study, such a sweeping conclusion is not supported by our results. We therefore did not alter our conclusion.

Other studies (Lieberman) show patients reaching improvement thresholds for a year after treatment initiation. Was each phase long enough?

We (had) addressed this as follows:
"Moreover, because we only followed patients on clozapine for 12 weeks, and the full treatment response may take several months to materialize, remission rates may have improved further had we followed our patients for longer.[18]"

We added to the Discussion:

"Fourth, it may be argued that a 4-week trial is not sufficiently long to decide whether to switch or not. However, a recent meta-analysis suggests this period is sufficient [(22)]."

Remission rates do not start at zero on two graphs.
The reviewer is right, however the first time point in these graphs is after the visit in which inclusion in the phase was determined, so some patients already were in remission at the first visit.

What is the evidence that amisulpride has less serious adverse effects?

We added to the Introduction:
"Although both drugs have multiple side-effects, in the case of amisulpride these are mostly limited to extrapyramidal symptoms and hyperprolactinaemia (although QTc prolongation can occur at higher doses), while those associated with olanzapine increase the risk of cardiovascular complications - and are therefore more serious in the long term than those associated with amisulpride[6]. It would therefore make sense to initiate treatment with amisulpride."

Findings of the Howes paper are mis-stated.

This was changed, also in response to reviewer 4. We now state:
However, in clinical practice the interval between the onset of treatment and the initiation of clozapine is as long as 10-12 years.[10]

Make a statement about capsule opacity.
This information has been added to the Methods section: 'Blinding was achieved by overencapsulating two 2.5 mg olanzapine tablets or one 200 mg amisulpride tablet into one capsule, utilizing the same manufacturing process to ensure that appearance, shape, smell, mass and taste of the opaque capsules were indistinguishable.'

The OPTiMiSE trial: a three-phase, double blind randomised switching study in first episode schizophrenia and schizophreniform disorder comparing amisulpride and olanzapine followed by open treatment with clozapine.

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Research in context

Evidence before this study

There is no established treatment algorithm for patients with schizophrenia. Fundamental questions about its treatment, such as whether switching antipsychotics improves outcome, remain unaddressed. PubMed was searched until Oct 2017 for randomized trials in which patients with schizophrenia, schizophreniform, or schizoaffective disorder (any diagnostic criteria) had been treated prospectively with a first antipsychotic drug. Nonresponders were subsequently randomized to either switching the antipsychotic or another pharmacological strategy. Search terms used were schizophreni* AND (antipsychot* OR neurolept* OR drug OR treat*) AND (switch* OR alternative* OR consecutive* OR subsequent OR shift OR change) AND (nonrespon* OR not respon* OR fail OR resistant* OR refract* OR ineffect*), article types "clinical trials" or "randomized controlled trials".

Added value of this study

This is the first study examining the relevance of switching antipsychotic medication in patients with first-episode schizophrenia who have not responded to their initial course of treatment.

Implications of all the available evidence

The results suggest that in the large majority of patients in the early stages of schizophrenia, symptomatic remission can be achieved using a simple treatment algorithm comprising the sequential administration of amisulpride and clozapine.

Summary

Background

It is not known whether switching antipsychotics or early use of clozapine improves outcome in (first-episode) schizophrenia.

Methods

The study was conducted in 27 centres in 14 European countries and Israel consisting of general hospitals and psychiatric specialty clinics. (Clinicaltrials.gov identifier is NCT01248195~~NCT01555814~~). Patients with schizophrenia or schizophreniform disorder were treated for four weeks with up to 800 mg/day amisulpride in an open design. Patients who did not meet symptomatic remission criteria at four weeks were randomized to continue amisulpride or switch to olanzapine (max 20 mg/day) during a six-week double blind phase. Patients who were not in remission at ten weeks were given clozapine (max 900 mg/day) for an additional 12 weeks in an open design. Data were analyzed using a generalised linear mixed model, with a logistic link and binomial error distribution.

Findings

Participants were recruited between May 26, 2011 and May 15, 2016 with 481 signing informed consent. Of the 446 patients in the ITT sample, 371 (83.2%) completed open amisulpride treatment, of whom 250 (~~56.1~~67.4%) were in remission. 93 of the patients who were not in remission continued to the six-week double-blind switching trial with 72 patients (77.4%) completing it (39 on olanzapine and 33 on amisulpride); 15 (45.5%) of the patients taking amisulpride reached remission versus 17 (43.6%) on olanzapine (p=.87~~9~~). Of the 40 patients who were not in remission after 10 weeks of treatment, 28 (70.0%) were started on clozapine; 18 patients (64.3%) completed the 12-week treatment, of whom five (~~17.9~~27.8%) met remission criteria.

Interpretation

In the large majority of patients in the early stages of schizophrenia, symptomatic remission can be achieved using a simple treatment algorithm comprising the sequential administration of amisulpride and clozapine.

~~Employing a treatment algorithm with a single antipsychotic for ten weeks and subsequent use of clozapine, remission can be achieved within 22 weeks in over three quarters of patients~~

~~with first-episode schizophrenia who complete treatment and almost two thirds of patients in whom treatment is initiated.~~

Funding

European Commission; 7th Program (HEALTH-F2-2010-242114).

Introduction

While effective antipsychotic medications have been available for over half a century, the application and implementation of these treatments is far from optimal. In particular, there is no established treatment algorithm for the use of antipsychotics in schizophrenia. In clinical practice, when a patient has not responded to the initial treatment, they are often switched from one antipsychotic medication to another. However, there is surprisingly little evidence that this improves clinical outcomes. Indeed, one of the most relevant questions in the treatment of the early phase of schizophrenia – and an essential ingredient in any treatment algorithm - is whether switching to another antipsychotic improves outcome when a patient has not responded to the treatment that was initiated.

Another aspect that has often been lacking in treatment studies in schizophrenia is a clinically relevant outcome measure. Generally, response to treatment has been defined as a reduction in the Positive and Negative Syndrome Scale (PANSS) total score of >20% but it has been argued that a more stringent outcome is 'remission', analogous to cancer treatment and reflecting an almost complete absence of the psychotic symptoms of schizophrenia.[1] This measure is clinically relevant and useful as an outcome in clinical trials.[2,3]

In a previous clinical trial, we found that amisulpride and olanzapine were comparably effective in the treatment of first episode schizophrenia[4] despite their different receptor-binding profiles[5-8]. These results are consistent with those of meta-analyses comparing the efficacy of antipsychotics in the treatment of schizophrenia[9-11]. In treatment algorithms, given equal effectiveness, one would choose to initiate treatment with the least toxic medication. Although both drugs have multiple side-effects, in the case of amisulpride these are mostly limited to extrapyramidal symptoms and hyperprolactinaemia (although QTc prolongation can occur at higher doses), while those associated with olanzapine increase the risk of cardiovascular complications - and are therefore more serious in the long term than those associated with amisulpride[9]. It would therefore make sense to initiate treatment with amisulpride.

In the minority of patients with schizophrenia who do not respond to antipsychotic medication, the intervention best supported by evidence is treatment with clozapine.[12] Current guidelines therefore recommend that clozapine be offered to patients who have not responded to two different antipsychotics, given at adequate doses for at least six weeks each. In theory, a first episode patient could therefore receive clozapine within 12 weeks after the start of treatment. However, in clinical practice the interval between the onset of treatment and the initiation of clozapine is as long as 10-12 years.[13]

The present study addressed two key issues: 1) In first-episode patients who do not respond to their first trial of antipsychotic medication, is switching to another antipsychotic effective? 2) Can earlier treatment with clozapine improve outcome in patients who have not remitted after 10 weeks of antipsychotic treatment~~a simple treatment algorithm facilitate the earlier initiation of treatment with clozapine~~?

Methods

Study design

The study comprised a combination of treatment designs: the first phase consisted of an open-label single-treatment arm, followed by a randomized, double blind phase. The third and final phase was again an open-label single-treatment arm. The study was conducted in 27 centres located in 14 European countries (Austria, Belgium, Bulgaria, Czech Republic, Denmark, France, Germany, Italy, the Netherlands, Poland, Romania, Spain, Switzerland and the United Kingdom) and Israel, consisting of general hospitals and psychiatric specialty clinics. Each country obtained ethics approval. The trial complied with the Declaration of Helsinki.[14] The University Medical Center Utrecht monitored the trial according to Good Clinical Practice and International Conference on Harmonization guidelines.[15] Clinicaltrials.gov identifier is NCT01248195~~NCT01555814~~.

Patients

Patients were recruited at the participating hospitals, from nearby healthcare facilities and through public advertisements. Eligible patients were aged 18–40 years and met criteria of the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) for schizophrenia, schizophreniform disorder, or schizoaffective disorder; diagnoses were confirmed by the Mini International Neuropsychiatric Interview plus (MINI-plus).[16] Female patients of childbearing potential were required to use a proper method of contraception. Patients were excluded if the time interval between the onset of psychosis and study entry exceeded two years; if any antipsychotic medication had been used for more than two weeks in the previous year and/or for a total of six weeks or more in their lifetime; if patients had a known intolerance to one of the study drugs; if patients met any of the contraindications for any of the study drugs as mentioned in the (local) package insert texts; if patients were coercively treated and/or represented by a legal guardian or under legal custody; or if patients were pregnant or breast feeding. All study participants provided written informed consent.

Randomisation and masking

The study design is shown in Figure 1 and described earlier in detail by Leucht and colleagues, including references for the scales used.[17]

The trial was divided into three treatment phases; patients were eligible for participation in the subsequent phase if they did not meet criteria of ‘symptomatic remission’ at the end of the

previous phase. 'Symptomatic remission' is based on the Andreasen criteria of remission, including the same items on the Positive and Negative Syndrome Scale. However, in contrast to the Andreasen criteria, the minimum duration of six months concerning the symptom severity was not applied.[1] All patients started with a four-week open label treatment with amisulpride 200-800 mg/day (Phase I). At the start of phase II, non-remitters from phase I were randomized 1:1 to double blind flexible dose treatment with olanzapine (5-20 mg/day) or amisulpride (200-800 mg/day). A randomisation table was generated by the Data Management department of the Julius Center, University Medical Center Utrecht, the Netherlands, using VB.Net with access to a SQL Server back end database. Study medication was packaged-in line with this randomisation table, using sequentially numbered kits. Randomization was performed online by a randomization website, also developed by the Julius Center, which provided the applicable kit number only. The application implemented stratification by site and gender, and applied the minimization method for randomization. The data management group was not involved in patient recruitment, which was conducted at each participating center. The complete study teams at each center as well as the participating patients were blind to treatment allocation. Blinding was achieved by overencapsulating two 2.5 mg olanzapine tablets or one 200 mg amisulpride tablet into one capsule, utilizing the same manufacturing process to ensure that appearance, shape, smell, mass and taste of the opaque capsules were indistinguishable. Olanzapine and amisulpride were purchased commercially and overencapsulated by Piramal Healthcare UK. Patients as well as study team members were masked to group assignment of each individual participant. Non-remitters in phase II continued into 12-week open label treatment with clozapine 100-900 mg/day (phase III).

Blood was drawn at the beginning and end of each treatment phase in order to relate proteomics, immune parameters and genetics to treatment outcome. In addition, patients who had remitted were randomised to a specific psychosocial intervention versus treatment as usual with the goal to improve adherence. The results from these studies are not yet available and will be reported separately. Finally, MRI and MRS assessments were conducted in a subsample of participants."

Procedures

After signing informed consent, the screening visit was conducted during which eligibility was assessed. Baseline data was obtained regarding demographics, diagnoses, present treatment setting, psychopathology (Positive and Negative Syndrome Scale; PANSS),

severity of illness (Clinical Global Impression; CGI), depression (Calgary Depression Scale for Schizophrenia; CDSS), personal and social functioning (Personal and Social Performance scale; PSP), subjective wellbeing (Subjective Wellbeing under Neuroleptic use; SWN), adverse effects (Udvalg for Kliniske Undersogelser; UKU), and alcohol and drug use. Frequency and severity of adverse events were assessed at each visit. In addition, weight, abdominal circumference and height were measured and an electrocardiogram was done as per amisulpride Summary of Product Characteristics. Data was collected at baseline and after 1, 2, 4, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 and 22 weeks, for most or all of the efficacy, safety and tolerability outcomes. Patients who did not meet remission criteria after completion of phase III, returned for a follow-up visit 48 weeks after baseline (26 weeks after the final phase III visit), where PANSS was assessed and rehospitalisation data was collected. For all patients who started phase I, a follow-up visit at 74 weeks post-baseline was scheduled to assess symptom severity and the current clinical diagnosis, as well as to collect data on hospitalisation.

Outcomes

The primary outcome measures were the symptomatic remission rates at the final visits of *phase I* (after four weeks of open treatment with amisulpride), *phase II* (after six weeks of double-blind treatment with amisulpride or olanzapine, comparison between arms) and *phase III* (after 12 weeks of open label treatment with clozapine). If remission criteria were met, the patient had completed the trial. If they were not met, the patient progressed to the next phase. Symptomatic remission was defined according to the criteria of Andreasen: eight specific symptoms rated by the PANSS (items P1, P2, P3, N1, N4, N6, G5 and G9) are at the most only mildly present (maximum rating of '3'), meaning that they do not interfere with daily life functioning.[15] All raters were certified through a standardised PANSS training and examination, provided by the sponsor. Halfway through the study, an inter-rater reliability assessment was conducted across all sites (ICC=0.82).

The main secondary outcome measure was a comparison between amisulpride and olanzapine on all-cause treatment discontinuation. Other secondary outcomes include the severity and improvement scores of the CGI, levels of depression (CDSS), personal and social functioning (PSP) and subjective wellbeing (SWN). Safety outcomes include the UKU side effects rating scale and weight gain.

Statistical analysis

Data of the EUFEST study[4] showed that about 40% of the patients on amisulpride were in symptomatic remission within four weeks. However, halfway through the study almost 60% of phase I patients met remission criteria. Subsequently, the power analysis was adjusted to the following: based on EUFEST we expect that 50% of the four-week non-responders who stay on amisulpride will be in symptomatic remission after another six weeks of treatment (10 weeks from treatment initiation). If the percentage of patients in remission increases from 50% to 70% as a result of switching to olanzapine (which is an estimation, as there are no prior studies on this topic), the two treatment arms will have to contain 90 patients each to obtain a statistical power of .79 with a type-I error rate of .05. If we consider that the drop out rate is approximately 30% and the remission rate 60% (both observations after 250 patients had been enrolled into the study), than this implies that at least 487 patients will have to be included at baseline, taking into account a drop-out of 30% during phase II (observation in first 50 phase II patients).

Remission, as assessed at the final visit of each phase, was first summarized as counts and percentages. Subsequently, remission at each visit was analysed using a generalised linear mixed model (GLMM), with a logistic link and binomial error distribution. Variables included were visit number as a categorical variable and the baseline PANSS score as a continuous covariate. In this way, all visits contributed to the estimate of the between patient variance, thereby making the estimate of remission at the final visit more robust while accounting for dropout. For phase II a comparison was made between the amisulpride and olanzapine arm, by including the treatment arm as a factor in the GLMM. The cumulative proportion of patients in remission over all three study phases was calculated using the number of patients in remission at the last visit of each phase, i.e. the phase completers in remission. We used the conservative assumption that dropouts within a phase did not reach remission throughout the study. Patients eligible for a next study phase, but not continuing into that phase, were assumed not to be different from patients who did continue. To assess the proportion of dropouts over time, a Kaplan Meier curve was used. Follow-up time was defined as the number of weeks between the date of the baseline visit and the date of the last visits of a patient. Patients who did not progress to a next phase because they were in remission were censored. Side effects were summarized per visit and per phase and expressed as percentages. Missing values were not imputed, as the GLMM analysis incorporates all available measurements, assuming that patients with available measurements are representative for all patients, including the patients with missing values. For side effects, we assumed that missing values indicated absence of side effects. All quantitative scores, including the PANNS, were summarized as means and standard deviation and differences

between groups were assessed by a t-test. Dichotomous variables were expressed as counts and percentages and differences between groups were assessed by Chi square tests. Differences between groups in proportions were calculated and a 95%CI according to Wilson's method. In all analyses, the criterion for statistical significance was $P < 0.05$. SPSS version 25 was used for all analyses. A Data Safety Monitoring Board oversaw the study.

Role of the funding sources

The funder of the study (FP7 EU) had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participants were recruited between May 26, 2011 and May 15, 2016. The final study visit took place on November 1, 2017. The trial was stopped on May 15, 2016, as the project end date was reached. Figure 2 shows the trial profile. 481 patients signed informed consent. In 16 patients (3.3%), the diagnosis could not be confirmed. Another 19 (4.0%) dropped out before the baseline visit for various reasons (n=7 screen failure; n=1 discontinuation of pre-existing antipsychotic unsuccessful; n=1 involuntary hospital admission; n=1 physician decision; n=9 changed their mind). Thus, 446 patients (92.7%) met diagnostic criteria and initiated the first phase: four-week open label treatment with amisulpride 200-800 mg daily. Baseline characteristics are displayed in Table 1 for the Intent To Treat (ITT) sample (n=446), as well as the subgroups of patients who continued into the subsequent treatment phase II (n=93) and phase III (n=28).

Phase I (4-week open amisulpride)

Out of the 446 patients in the ITT sample who initiated the open label amisulpride treatment phase, 371 completed the four-week treatment (83.2%). A total of 250 patients met remission criteria at end of phase I, a remission rate of 67.4% amongst completers. The remission rate within the whole ITT sample (n=446) was 56.1%, when patients without a known remission status at the end of phase I were categorized as non-remitters. Figure 3 shows the remission rates over the course of phase I. Symptom scores and changes in weight are shown in Table 4.

There was no significant difference between remitters and non-remitters in gender (30.4% versus 24.0% female respectively, P=.20), but they did differ in age (26.3 [SD 6.3] vs 24.5 [SD 5.4] years respectively; p=.004); duration of the current psychotic episode (6.0 [SD 6.0] vs 7.7 [SD 7.0] months respectively, p=.025) and age at onset (25.9 [SD 6.3) and 23.8 [SD 5.4] years, respectively p=.001).

The mean amisulpride dose at the end of Phase I was 490.4 mg/day (SD 207.4); in the remitters it was 463.8 mg/day (SD 196.0) and 535.2 md/day (SD 209.2; p=.001) in the non remitters. Remitters were more likely to have a diagnosis of schizophreniform disorder (44.0% versus 33.1% for non-remitters, p=.044) and less likely to have a diagnosis of schizophrenia (52.0% versus 71.1% for non-remitters, p<.001). No differences in alcohol dependency or substance abuse were found.

Phase II (6-week double blind switching vs continuation)

Of the 121 non-remitters at the end of phase I, 93 (76.9%) continued to phase II, in which they were randomized 1:1 to 6 weeks of continued treatment with amisulpride (n=47), or they were switched to 6 weeks of treatment with olanzapine (n=46). 28 phase I non-remitters decided not to continue into phase II for various reasons (refer to Figure 2); this subgroup had a shorter duration of illness (5.6 [SD 5.3] months versus 8.4 [SD 7.3] months, respectively; p=.040) than those who initiated phase II treatment, but there were no significant differences in gender, age, diagnosis, or alcohol / substance abuse. Baseline characteristics of the 93 patients for the two treatment groups are depicted in Table 5. There were no statistically significant differences in proportion or means between the two randomized groups.

Of the 93 patients randomized, 72 completed phase II (77.4%): 33 taking amisulpride versus 39 taking olanzapine. At the end of phase II, 32 patients met remission criteria, an overall remission rate amongst completers of 44.4%. Within the IIT sample, the remission rate was 35.5%. Remission rates per treatment arm over the phase II visits are depicted in Figure 4. There was no significant difference in remission rate between the two treatment arms: the rate for amisulpride was 45.5% (n=15) versus 43.6% (n=17) for olanzapine (P=.87). Symptom scores and changes in weight are shown in Table 4. The mean dose of amisulpride at the end of Phase II was 590.9 mg/day (SD 236.1); remitters 586.7 mg/day (SD 220.0), non remitters 600.0 mg/day (SD 237.6; p=.87) The mean dose of olanzapine at the end of Phase II was 15.6 mg/day (SD 6.5); remitters 14.4 mg/day (SD 5.6), non-remitters 17.5 (SD 6.3; p=.12).

A logistic generalized linear model was used to analyze the remission data using all three repeated PANSS assessments, while adjusting for the PANSS score at the start of phase II (week four; phase II baseline). The odds ratio for meeting remission criteria at the end of phase II for amisulpride relative to olanzapine was 1.07 (95% CI: 0.38 to 2.96). Using a linear mixed model, PANSS scores at the end of phase II were compared between treatment groups, again adjusting for the PANSS score at the start of phase II (phase II baseline). The reduction in PANSS score was not significantly different between treatments; the phase II baseline-corrected difference for amisulpride relative to olanzapine was -3.24 (95% CI: -10.07 to 3.60, P=.35).

Dropout rates between the two treatment arms did not differ significantly, although there was a trend in favor of olanzapine; 29.8% of patients randomized to amisulpride dropped out (n=14) versus 15.2 % (n=7) on olanzapine, a difference of 14.5%, 95%CI -2.5% to 30.7% (p=.093). Patients treated with olanzapine gained significantly more weight than patients treated with amisulpride: 4.40 (SD 3.65) kg versus 2.29 (SD 3.07) kg (P=.021). Otherwise, the two treatment arms did not differ on the incidence of side effects, corrected for phase II baseline assessments.

Phase III (12-week open clozapine)

Of the 40 phase II non-remitters, 12 patients (30.0%) decided not to continue into the 12-week open label phase III for various reasons (refer to Figure 2). A further ten patients dropped out during phase III (drop-out rate during phase III 35.7%), leaving a total of 18 patients who completed the clozapine treatment. Five patients met remission criteria, resulting in a remission rate of 27.8% among those who completed treatment. Within the IIT sample (which classified dropouts as not meeting remission criteria), the remission rate was 17.9%;

Despite the relatively low remission rate, patients demonstrated symptom improvement during clozapine treatment, as shown in Figure 6. The phase III completers improved a total of 24.9 points on the PANSS score relative to study baseline (visit 2: p<.001) and 18.4 points relative to the phase III baseline (at week ten: p=.002). The mean dose of clozapine at the end of Phase III was 279.0 mg/day (SD 130.2); remitters 280.0 mg/day (SD 115.1), non remitters 317.3 (SD 146.7; p=.62). Clozapine blood concentration was assessed at the end of phase III. Remitters (n=5) had a mean clozapine blood concentration of 321 ng/ml (SD 226), non-remitters (n=13) had a mean clozapine concentration of 350 ng/ml (SD 391).

Phase I-III

Out of the 446 patient who initiated the first treatment phase, a total of 287 patients met remission criteria at one of the three treatment phases, adding up to an overall remission rate of 64.3% after a maximum of 20 treatment weeks. The cumulative remission rate based on the completers of the three phases was 76.4%. Figure 6 shows a steady decline in the mean total PANSS scores over the course of each individual treatment phase. In supplemental Figure 1, the Kaplan-Meier curve for dropout over time is depicted. After 20 week of follow-up, the proportion still under study, censoring for remission, was still 0.651.

The mean doses of amisulpride, olanzapine and clozapine in the three treatment phases are included in Table 2; for drop outs, the dose at the last visit has been used. The use of concomitant medication in each phase is shown in Table 3.

Sexual dysfunction and extrapyramidal symptoms are reported in Table 4. Weight changes included in Table 4 are relative to the baseline of the corresponding study phase. An extensive report of all side effects reported is provided in a table in the appendix. The incidence of Serious Adverse Events did not differ between the treatment arms in phase II: one patient randomized to olanzapine was hospitalized due to an epileptic seizure, and one patient randomized to amisulpride was hospitalized twice during phase II due to exacerbations of psychotic symptoms. Over the course of the trial, two serious suicide attempts were reported. One resulted in the only death during the trial, seven days after discontinuing amisulpride. The other attempt was during amisulpride treatment in phase I.

48-week follow-up visit

For patients who did not meet remission criteria after completion of phase III, a follow-up visit was scheduled, 48 weeks post- baseline (26 weeks after the final phase III visit). Out of the 11 non-remitters at the end of phase III, 8 patients returned for this visit. The mean total PANSS score was 70.5 (SD 22.3), ranging from 40 to 104. Three patients met remission criteria during this visit. None of the patients were rehospitalised since the end of phase III.

74-week follow-up visit

For all patients who entered phase I, a follow-up visit was scheduled 74 weeks post-baseline. This visit was conducted for 167 patients. The diagnosis at that time point was established: 13 patients (7.8%) were diagnosed with schizophreniform disorder, 22 patients (13.2%) with schizoaffective disorder, 123 patients (73.7%) with schizophrenia and 9 patients (5.3%) received other diagnoses (e.g. psychosis NOS, bipolar disorder, unspecified non-organic psychosis). PANSS data was available for 140 patients; the mean total PANSS score was 50.2 (SD 15.0, range 30-105). 95 patients (56.9%) met remission criteria. Seventeen out of 140 patients (10.2%) were hospitalized at least once since the most recent study visit.

Discussion

Our first major finding is that switching from amisulpride to olanzapine in first-episode schizophrenia did not improve clinical outcome. In fact, of the 93 patients who were randomized an almost equal proportion (45%) achieved remission whether they continued treatment with amisulpride or were switched to olanzapine. Moreover, the clinical outcome in the two groups was also similar when this was defined in terms of symptomatic improvement (as a continuous variable). Extrapolating, these data suggest that if a patient fails to achieve remission on their first antipsychotic drug, switching to a different drug is no more effective than remaining on the same medication and waiting to see if remission is achieved at a later stage.

To our knowledge, this is the first study to examine the effects of switching antipsychotics in patients with (first-episode) schizophrenia who do not respond to their initial antipsychotic treatment (response has been defined differently in the various studies; we used remission in the current study). With the exception of one study, all previous studies were conducted in the later, chronic, stage of the illness. Moreover, the single study in first-episode schizophrenia did not assess whether switching was more effective than staying on the original treatment (for review see[17]). That study[18] compared risperidone and olanzapine in 287 patients with first-episode schizophrenia in a non-randomized, open design~~, with the patient's clinician selecting which medication was used first~~. Response was defined as much improved or better on the CGI. Patients who failed to meet response criteria after four weeks were switched to the other antipsychotic; thus switching versus staying on the first medication was not examined. Clozapine was given when there was no response to both antipsychotics. In that study, 75% of patients met response criteria after four weeks, with more responding to olanzapine (82%) than to risperidone (66%). In the second phase of the study, response rates dropped to 17%, with olanzapine again doing better than risperidone. Important differences compared to the present study were that the first antipsychotic was selected by the treating clinician, the definition of response was less stringent, and switching was open. Moreover, it is unclear whether data were analysed on the basis of completers only or whether an ITT analysis was done.

The only double-blind study that compared switching versus continuation in non-responders was conducted in patients with chronic schizophrenia (age around 42 years). Response in the

first two weeks was defined as ≥20% reduction in total PANSS scores. This corresponds to a lesser degree of clinical improvement than the symptomatic remission criterion used in the present study.[19] Patients who did not respond to a two-week open trial with risperidone (2-6 mg/day) were randomized to either continuing on risperidone or were switched to olanzapine (10-20 mg/day). Switching resulted in a small but significantly greater reduction in total PANSS scores after four weeks. ~~However, response in the first two weeks was defined as ≥20% reduction in total PANSS scores. This corresponds to a lesser degree of clinical improvement than the symptomatic remission criterion used in the present study.[17]~~

In the current study, after ten weeks of treatment most of the patients were either in symptomatic remission or had dropped out, leaving only 28 of the initial 446 patients (6.3%) eligible for switching to clozapine. Although only five patients treated with clozapine reached remission, there was still a substantial symptomatic improvement in the sample overall, with an average reduction in total PANSS scores of more than 18 points. These results suggest that providing clozapine early in the treatment of patients with first episode schizophrenia may result in clinical improvement, even if this is short of full symptomatic remission. Moreover, because we only followed patients on clozapine for 12 weeks, and the full treatment response may take several months to materialize, remission rates may have improved further had we followed our patients for longer.[20]

Symptomatic remission rates in our study were high: after only four weeks of (open) treatment with amisulpride, 56% of all 446 patients had reached remission, even when assuming that all drop outs were non-remitters; the remission rate increased to 67% when the analysis was restricted to patients who completed the initial 4-week treatment period. This proportion is impressive for two reasons: first, it corresponds to clinical remission, and not just a numerical reduction of symptoms on a rating scale; second, remission was achieved after only four weeks of treatment. Our results therefore suggest that a majority of patients show a clinically meaningful improvement after only a few weeks of treatment - corroborated by the reduction in the Clinical Global Improvement scale. An additional six weeks of treatment led to more improvement, with a further 45% of patients (in both arms) achieving remission. However, because this was based on a smaller sample (due to the high initial remission rate and the drop out between phases), the total remission rate in completers calculated from baseline at the end of Phase II was 65%. Additional treatment with clozapine increased the cumulative remission rate to 76% - again assuming all drop-outs did not achieve

remission. This indicates that for the large majority of patients with first episode of schizophrenia, a rapid and (almost) complete symptomatic recovery can be expected with antipsychotic treatment. The high and rapidly occuring symptomatic response found here is consistent with results reported in other studies in first episode schizophrenia.[21,22] Nevertheless, some first-episode patients will respond only after continuous treatment lasting up to eight weeks.[23]

The doses of antipsychotics used in the present study are consistent with those generally administered in first episode schizophrenia; amisulpride was given in a mean dose of 591 mg/day, olanzapine 15.6 mg/day and clozapine 279 mg/day (with blood levels a little under 350 ng/L). Critically, the doses in remitters and non-remitters were similar, with those in the non-remitters numerically higher in all phases for all drugs, suggesting that non-remission was not attributable to underdosing. Similarly, although the clozapine dose given was relatively low (280-300 mg/day), blood levels in the non-remitters were adequate (> 350 ng/L), so the low remission rate is unlikely to be related to inadequate dosing. Moreover, the clozapine dose we used was comparable to that given in the first-episode study by Lieberman et. al.[20] where 80% of patients on clozapine reached remission.

Side effects were as expected: amisulpride was associated with extrapyramidal side effects and those related to increased prolactin levels; olanzapine and clozapine induced substantial weight gain, even over the relatively short six and twelve-week periods of treatment, respectively. In phase II, side effects were more prominent in the patients on olanzapine compared to amisulpride: this may have been because those intolerant to amisulpride had dropped out in the earlier phase or had developed tolerance. All drugs were associated with a substantial gain in weight over the course of treatment, although it was most pronounced on olanzapine and clozapine.

The results should be viewed in the context of the study's limitations. First, the sample in the second, randomized phase (II) was relatively modest, comprising 93 patients. This was more the result of the high remission rate in Phase I than the number of dropouts, which was less than 17%. However, remission rates in the amisulpride and olanzapine arms were virtually identical, suggesting a larger sample size may not have changed the results. Second, both the initial treatment with amisulpride and the subsequent one with clozapine were open label. This may have increased the remission rates in both phases. It was felt though, that the initial

treatment should be pragmatic, reflecting clinical reality as much as possible, whereas the comparison between two drugs in Phase II needed to be as un-biased as possible and therefore double blind. Third, it could be argued that a comparison between continuation with amisulpride and switching to clozapine in Phase III would have been of interest; the current design cannot address that question. Indeed, whether clozapine has an added benefit over continuation with amisulpride after ten weeks of its use needs further study. Fourth, it may be argued that a 4-week trial is not sufficiently long to decide whether to switch or not. However, a recent meta-analysis suggests this period is sufficient[24]. Finally, although our results show that a large majority of first-episode schizophrenia patients reaches remission within a few months of treatment, failing to stay in remission remains a major impediment in the treatment of schizophrenia[25].

Current guidelines recommend that clozapine should be offered to patients who have not responded to treatment with two different antipsychotics. However, if the likelihood of non response to one antipsychotic given for a sufficient length of time is similar to that with two courses of different antipsychotics, it may be feasible to define non-response (operationalized as failure to achieve symptomatic remission) on the basis of a single course of antipsychotic treatment, as long as it is given for long enough. Adopting a simpler treatment algorithm with one course of antipsychotic treatment would allow these patients to be identified earlier and reduce the delay before they can be treated with clozapine.

In summary, our results suggest that switching antipsychotics in minimally treated patients with first-episode schizophrenia does not improve outcome in those who are not in symptomatic remission after their first antipsychotic regimen. Although switching to clozapine early in the treatment did not dramatically improve remission rates, it did result in a substantial improvement in symptoms, albeit that many first-episode patients did not tolerate the side effects associated with its treatment.

Employing an algorithm of treatment with a single antipsychotic for up to ten weeks and subsequent use of clozapine in non-remitters, remission can be achieved within 22 weeks for over three quarters of first-episode patients who complete treatment and for almost two thirds of patients where treatment was initiated. Although these results need to be replicated and broadened (using different antipsychotics), they suggest that achieving remission in the early stages of schizophrenia is possible in the large majority of patients using a simple treatment algorithm of sequential use of amisulpride and clozapine.

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Contributors

RSK, SK, IES, IWR, SL, SH and WWF designed the study. RSK and SK obtained funding. RSK supervised the study. MJCE, RSK and IWR analyzed and interpreted the data. RSK, IWR and MJCE drafted the report. RSK, IWR, SL, PM, SWL, ML, CA, PD, RD, CM, SH, DR, MW, SG, BG, WWF and IES participated in the collection of data. All authors participated in the critical revision of the report and approved the final report.

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Declaration of interests

-René S. Kahn: personal fees for consultancy from Alkermes, Minerva Neuroscience, Gedeon-Richter and Otsuka; personal fees from Otsuka/Lundbeck as speaker

-Inge Winter van Rossum, Paola Dazzan, Philip McGuire, Richard Drake, Dan Rujescu, Mark Weiser, Shitij Kapur, Marion Leboyer have nothing to disclose.

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The OPTiMiSE trial: a three-phase, double blind randomised switching study in first episode schizophrenia and schizophreniform disorder comparing amisulpride and olanzapine followed by open treatment with clozapine.

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Research in context

Evidence before this study

There is no established treatment algorithm for patients with schizophrenia. Fundamental questions about its treatment, such as whether switching antipsychotics improves outcome, remain unaddressed. PubMed was searched until Oct 2017 for randomized trials in which patients with schizophrenia, schizophreniform, or schizoaffective disorder (any diagnostic criteria) had been treated prospectively with a first antipsychotic drug. Nonresponders were subsequently randomized to either switching the antipsychotic or another pharmacological strategy. Search terms used were schizophreni* AND (antipsychot* OR neurolept* OR drug OR treat*) AND (switch* OR alternative* OR consecutive* OR subsequent OR shift OR change) AND (nonrespon* OR not respon* OR fail OR resistant* OR refract* OR ineffect*), article types "clinical trials" or "randomized controlled trials".

Added value of this study

This is the first study examining the relevance of switching antipsychotic medication in patients with first-episode schizophrenia who have not responded to their initial course of treatment.

Implications of all the available evidence

The results suggest that in the large majority of patients in the early stages of schizophrenia, symptomatic remission can be achieved using a simple treatment algorithm comprising the sequential administration of amisulpride and clozapine.

Summary

Background

It is not known whether switching antipsychotics or early use of clozapine improves outcome in (first-episode) schizophrenia.

Methods

The study was conducted in 27 centres in 14 European countries and Israel consisting of general hospitals and psychiatric specialty clinics. (Clinicaltrials.gov identifier is NCT01248195). Patients with schizophrenia or schizophreniform disorder were treated for four weeks with up to 800 mg/day amisulpride in an open design. Patients who did not meet symptomatic remission criteria at four weeks were randomized to continue amisulpride or switch to olanzapine (max 20 mg/day) during a six-week double blind phase. Patients who were not in remission at ten weeks were given clozapine (max 900 mg/day) for an additional 12 weeks in an open design. Data were analyzed using a generalised linear mixed model, with a logistic link and binomial error distribution.

Findings

Participants were recruited between May 26, 2011 and May 15, 2016 with 481 signing informed consent. Of the 446 patients in the ITT sample, 371 (83.2%) completed open amisulpride treatment, of whom 250 (67.4%) were in remission. 93 of the patients who were not in remission continued to the six-week double-blind switching trial with 72 patients (77.4%) completing it (39 on olanzapine and 33 on amisulpride); 15 (45.5%) of the patients taking amisulpride reached remission versus 17 (43.6%) on olanzapine (p=.87). Of the 40 patients who were not in remission after 10 weeks of treatment, 28 (70.0%) were started on clozapine; 18 patients (64.3%) completed the 12-week treatment, of whom five (27.8%) met remission criteria.

Interpretation

In the large majority of patients in the early stages of schizophrenia, symptomatic remission can be achieved using a simple treatment algorithm comprising the sequential administration of amisulpride and clozapine.

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Introduction

While effective antipsychotic medications have been available for over half a century, the application and implementation of these treatments is far from optimal. In particular, there is no established treatment algorithm for the use of antipsychotics in schizophrenia. In clinical practice, when a patient has not responded to the initial treatment, they are often switched from one antipsychotic medication to another. However, there is surprisingly little evidence that this improves clinical outcomes. Indeed, one of the most relevant questions in the treatment of the early phase of schizophrenia – and an essential ingredient in any treatment algorithm - is whether switching to another antipsychotic improves outcome when a patient has not responded to the treatment that was initiated.

Another aspect that has often been lacking in treatment studies in schizophrenia is a clinically relevant outcome measure. Generally, response to treatment has been defined as a reduction in the Positive and Negative Syndrome Scale (PANSS) total score of >20% but it has been argued that a more stringent outcome is 'remission', analogous to cancer treatment and reflecting an almost complete absence of the psychotic symptoms of schizophrenia.[1] This measure is clinically relevant and useful as an outcome in clinical trials.[2,3]

In a previous clinical trial, we found that amisulpride and olanzapine were comparably effective in the treatment of first episode schizophrenia[4] despite their different receptor-binding profiles[5-8]. These results are consistent with those of meta-analyses comparing the efficacy of antipsychotics in the treatment of schizophrenia[9-11]. In treatment algorithms, given equal effectiveness, one would choose to initiate treatment with the least toxic medication. Although both drugs have multiple side-effects, in the case of amisulpride these are mostly limited to extrapyramidal symptoms and hyperprolactinaemia (although QTc prolongation can occur at higher doses), while those associated with olanzapine increase the risk of cardiovascular complications - and are therefore more serious in the long term than those associated with amisulpride[9]. It would therefore make sense to initiate treatment with amisulpride.

In the minority of patients with schizophrenia who do not respond to antipsychotic medication, the intervention best supported by evidence is treatment with clozapine.[12] Current guidelines therefore recommend that clozapine be offered to patients who have not responded to two different antipsychotics, given at adequate doses for at least six weeks each. In theory, a first episode patient could therefore receive clozapine within 12 weeks after the start of treatment. However, in clinical practice the interval between the onset of treatment and the initiation of clozapine is as long as 10-12 years.[13]

The present study addressed two key issues: 1) In first-episode patients who do not respond to their first trial of antipsychotic medication, is switching to another antipsychotic effective? 2) Can earlier treatment with clozapine improve outcome in patients who have not remitted after 10 weeks of antipsychotic treatment?

Methods

Study design

The study comprised a combination of treatment designs: the first phase consisted of an open-label single-treatment arm, followed by a randomized, double blind phase. The third and final phase was again an open-label single-treatment arm. The study was conducted in 27 centres located in 14 European countries (Austria, Belgium, Bulgaria, Czech Republic, Denmark, France, Germany, Italy, the Netherlands, Poland, Romania, Spain, Switzerland and the United Kingdom) and Israel, consisting of general hospitals and psychiatric specialty clinics. Each country obtained ethics approval. The trial complied with the Declaration of Helsinki.[14] The University Medical Center Utrecht monitored the trial according to Good Clinical Practice and International Conference on Harmonization guidelines.[15] Clinicaltrials.gov identifier is NCT01248195.

Patients

Patients were recruited at the participating hospitals, from nearby healthcare facilities and through public advertisements. Eligible patients were aged 18–40 years and met criteria of the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) for schizophrenia, schizophreniform disorder, or schizoaffective disorder; diagnoses were confirmed by the Mini International Neuropsychiatric Interview plus (MINI-plus).[16] Female patients of childbearing potential were required to use a proper method of contraception. Patients were excluded if the time interval between the onset of psychosis and study entry exceeded two years; if any antipsychotic medication had been used for more than two weeks in the previous year and/or for a total of six weeks or more in their lifetime; if patients had a known intolerance to one of the study drugs; if patients met any of the contraindications for any of the study drugs as mentioned in the (local) package insert texts; if patients were coercively treated and/or represented by a legal guardian or under legal custody; or if patients were pregnant or breast feeding. All study participants provided written informed consent.

Randomisation and masking

The study design is shown in Figure 1 and described earlier in detail by Leucht and colleagues, including references for the scales used.[17]

The trial was divided into three treatment phases; patients were eligible for participation in the subsequent phase if they did not meet criteria of ‘symptomatic remission’ at the end of the

previous phase. ‘Symptomatic remission’ is based on the Andreasen criteria of remission, including the same items on the Positive and Negative Syndrome Scale. However, in contrast to the Andreasen criteria, the minimum duration of six months concerning the symptom severity was not applied.[1] All patients started with a four-week open label treatment with amisulpride 200-800 mg/day (Phase I). At the start of phase II, non-remitters from phase I were randomized 1:1 to double blind flexible dose treatment with olanzapine (5-20 mg/day) or amisulpride (200-800 mg/day). A randomisation table was generated by the Data Management department of the Julius Center, University Medical Center Utrecht, the Netherlands, using VB.Net with access to a SQL Server back end database. Study medication was packaged-in line with this randomisation table, using sequentially numbered kits. Randomization was performed online by a randomization website, also developed by the Julius Center, which provided the applicable kit number only. The application implemented stratification by site and gender, and applied the minimization method for randomization. The data management group was not involved in patient recruitment, which was conducted at each participating center. The complete study teams at each center as well as the participating patients were blind to treatment allocation. Blinding was achieved by overencapsulating two 2.5 mg olanzapine tablets or one 200 mg amisulpride tablet into one capsule, utilizing the same manufacturing process to ensure that appearance, shape, smell, mass and taste of the opaque capsules were indistinguishable. Olanzapine and amisulpride were purchased commercially and overencapsulated by Piramal Healthcare UK. Patients as well as study team members were masked to group assignment of each individual participant. Non-remitters in phase II continued into 12-week open label treatment with clozapine 100-900 mg/day (phase III).

Blood was drawn at the beginning and end of each treatment phase in order to relate proteomics, immune parameters and genetics to treatment outcome. In addition, patients who had remitted were randomised to a specific psychosocial intervention versus treatment as usual with the goal to improve adherence. The results from these studies are not yet available and will be reported separately. Finally, MRI and MRS assessments were conducted in a subsample of participants.”

Procedures

After signing informed consent, the screening visit was conducted during which eligibility was assessed. Baseline data was obtained regarding demographics, diagnoses, present treatment setting, psychopathology (Positive and Negative Syndrome Scale; PANSS),

severity of illness (Clinical Global Impression; CGI), depression (Calgary Depression Scale for Schizophrenia; CDSS), personal and social functioning (Personal and Social Performance scale; PSP), subjective wellbeing (Subjective Wellbeing under Neuroleptic use; SWN), adverse effects (Udvalg for Kliniske Undersogelser; UKU), and alcohol and drug use. Frequency and severity of adverse events were assessed at each visit. In addition, weight, abdominal circumference and height were measured and an electrocardiogram was done as per amisulpride Summary of Product Characteristics. Data was collected at baseline and after 1, 2, 4, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 and 22 weeks, for most or all of the efficacy, safety and tolerability outcomes. Patients who did not meet remission criteria after completion of phase III, returned for a follow-up visit 48 weeks after baseline (26 weeks after the final phase III visit), where PANSS was assessed and rehospitalisation data was collected. For all patients who started phase I, a follow-up visit at 74 weeks post-baseline was scheduled to assess symptom severity and the current clinical diagnosis, as well as to collect data on hospitalisation.

Outcomes

The primary outcome measures were the symptomatic remission rates at the final visits of *phase I* (after four weeks of open treatment with amisulpride), *phase II* (after six weeks of double-blind treatment with amisulpride or olanzapine, comparison between arms) and *phase III* (after 12 weeks of open label treatment with clozapine). If remission criteria were met, the patient had completed the trial. If they were not met, the patient progressed to the next phase. Symptomatic remission was defined according to the criteria of Andreasen: eight specific symptoms rated by the PANSS (items P1, P2, P3, N1, N4, N6, G5 and G9) are at the most only mildly present (maximum rating of '3'), meaning that they do not interfere with daily life functioning.[15] All raters were certified through a standardised PANSS training and examination, provided by the sponsor. Halfway through the study, an inter-rater reliability assessment was conducted across all sites (ICC=0.82).

The main secondary outcome measure was a comparison between amisulpride and olanzapine on all-cause treatment discontinuation. Other secondary outcomes include the severity and improvement scores of the CGI, levels of depression (CDSS), personal and social functioning (PSP) and subjective wellbeing (SWN). Safety outcomes include the UKU side effects rating scale and weight gain.

Statistical analysis

Data of the EUFEST study[4] showed that about 40% of the patients on amisulpride were in symptomatic remission within four weeks. However, halfway through the study almost 60% of phase I patients met remission criteria. Subsequently, the power analysis was adjusted to the following: based on EUFEST we expect that 50% of the four-week non-responders who stay on amisulpride will be in symptomatic remission after another six weeks of treatment (10 weeks from treatment initiation). If the percentage of patients in remission increases from 50% to 70% as a result of switching to olanzapine (which is an estimation, as there are no prior studies on this topic), the two treatment arms will have to contain 90 patients each to obtain a statistical power of .79 with a type-I error rate of .05. If we consider that the drop out rate is approximately 30% and the remission rate 60% (both observations after 250 patients had been enrolled into the study), than this implies that at least 487 patients will have to be included at baseline, taking into account a drop-out of 30% during phase II (observation in first 50 phase II patients).

Remission, as assessed at the final visit of each phase, was first summarized as counts and percentages. Subsequently, remission at each visit was analysed using a generalised linear mixed model (GLMM), with a logistic link and binomial error distribution. Variables included were visit number as a categorical variable and the baseline PANSS score as a continuous covariate. In this way, all visits contributed to the estimate of the between patient variance, thereby making the estimate of remission at the final visit more robust while accounting for dropout. For phase II a comparison was made between the amisulpride and olanzapine arm, by including the treatment arm as a factor in the GLMM. The cumulative proportion of patients in remission over all three study phases was calculated using the number of patients in remission at the last visit of each phase, i.e. the phase completers in remission. We used the conservative assumption that dropouts within a phase did not reach remission throughout the study. Patients eligible for a next study phase, but not continuing into that phase, were assumed not to be different from patients who did continue. To assess the proportion of dropouts over time, a Kaplan Meier curve was used. Follow-up time was defined as the number of weeks between the date of the baseline visit and the date of the last visits of a patient. Patients who did not progress to a next phase because they were in remission were censored. Side effects were summarized per visit and per phase and expressed as percentages. Missing values were not imputed, as the GLMM analysis incorporates all available measurements, assuming that patients with available measurements are representative for all patients, including the patients with missing values. For side effects, we assumed that missing values indicated absence of side effects. All quantitative scores, including the PANNS, were summarized as means and standard deviation and differences

between groups were assessed by a t-test. Dichotomous variables were expressed as counts and percentages and differences between groups were assessed by Chi square tests. Differences between groups in proportions were calculated and a 95%CI according to Wilson's method. In all analyses, the criterion for statistical significance was $P < 0.05$. SPSS version 25 was used for all analyses. A Data Safety Monitoring Board oversaw the study.

Role of the funding sources

The funder of the study (FP7 EU) had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participants were recruited between May 26, 2011 and May 15, 2016. The final study visit took place on November 1, 2017. The trial was stopped on May 15, 2016, as the project end date was reached. Figure 2 shows the trial profile. 481 patients signed informed consent. In 16 patients (3.3%), the diagnosis could not be confirmed. Another 19 (4.0%) dropped out before the baseline visit for various reasons (n=7 screen failure; n=1 discontinuation of pre-existing antipsychotic unsuccessful; n=1 involuntary hospital admission; n=1 physician decision; n=9 changed their mind). Thus, 446 patients (92.7%) met diagnostic criteria and initiated the first phase: four-week open label treatment with amisulpride 200-800 mg daily. Baseline characteristics are displayed in Table 1 for the Intent To Treat (ITT) sample (n=446), as well as the subgroups of patients who continued into the subsequent treatment phase II (n=93) and phase III (n=28).

Phase I (4-week open amisulpride)

Out of the 446 patients in the ITT sample who initiated the open label amisulpride treatment phase, 371 completed the four-week treatment (83.2%). A total of 250 patients met remission criteria at end of phase I, a remission rate of 67.4% amongst completers. The remission rate within the whole ITT sample (n=446) was 56.1%, when patients without a known remission status at the end of phase I were categorized as non-remitters. Figure 3 shows the remission rates over the course of phase I. Symptom scores and changes in weight are shown in Table 4.

There was no significant difference between remitters and non-remitters in gender (30.4% versus 24.0% female respectively, P=.20), but they did differ in age (26.3 [SD 6.3] vs 24.5 [SD 5.4] years respectively; p=.004); duration of the current psychotic episode (6.0 [SD 6.0] vs 7.7 [SD 7.0] months respectively, p=.025) and age at onset (25.9 [SD 6.3) and 23.8 [SD 5.4] years, respectively p=.001).

The mean amisulpride dose at the end of Phase I was 490.4 mg/day (SD 207.4); in the remitters it was 463.8 mg/day (SD 196.0) and 535.2 md/day (SD 209.2; p=.001) in the non remitters. Remitters were more likely to have a diagnosis of schizophreniform disorder (44.0% versus 33.1% for non-remitters, p=.044) and less likely to have a diagnosis of schizophrenia (52.0% versus 71.1% for non-remitters, p<.001). No differences in alcohol dependency or substance abuse were found.

Phase II (6-week double blind switching vs continuation)

Of the 121 non-remitters at the end of phase I, 93 (76.9%) continued to phase II, in which they were randomized 1:1 to 6 weeks of continued treatment with amisulpride (n=47), or they were switched to 6 weeks of treatment with olanzapine (n=46). 28 phase I non-remitters decided not to continue into phase II for various reasons (refer to Figure 2); this subgroup had a shorter duration of illness (5.6 [SD 5.3] months versus 8.4 [SD 7.3] months, respectively; p=.040) than those who initiated phase II treatment, but there were no significant differences in gender, age, diagnosis, or alcohol / substance abuse. Baseline characteristics of the 93 patients for the two treatment groups are depicted in Table 5. There were no statistically significant differences in proportion or means between the two randomized groups.

Of the 93 patients randomized, 72 completed phase II (77.4%): 33 taking amisulpride versus 39 taking olanzapine. At the end of phase II, 32 patients met remission criteria, an overall remission rate amongst completers of 44.4%. Within the IIT sample, the remission rate was 35.5%. Remission rates per treatment arm over the phase II visits are depicted in Figure 4. There was no significant difference in remission rate between the two treatment arms: the rate for amisulpride was 45.5% (n=15) versus 43.6% (n=17) for olanzapine (P=.87). Symptom scores and changes in weight are shown in Table 4. The mean dose of amisulpride at the end of Phase II was 590.9 mg/day (SD 236.1); remitters 586.7 mg/day (SD 220.0), non remitters 600.0 mg/day (SD 237.6; p=.87) The mean dose of olanzapine at the end of Phase II was 15.6 mg/day (SD 6.5); remitters 14.4 mg/day (SD 5.6), non-remitters 17.5 (SD 6.3; p=.12).

A logistic generalized linear model was used to analyze the remission data using all three repeated PANSS assessments, while adjusting for the PANSS score at the start of phase II (week four; phase II baseline). The odds ratio for meeting remission criteria at the end of phase II for amisulpride relative to olanzapine was 1.07 (95% CI: 0.38 to 2.96). Using a linear mixed model, PANSS scores at the end of phase II were compared between treatment groups, again adjusting for the PANSS score at the start of phase II (phase II baseline). The reduction in PANSS score was not significantly different between treatments; the phase II baseline-corrected difference for amisulpride relative to olanzapine was -3.24 (95% CI: -10.07 to 3.60, P=.35).

Dropout rates between the two treatment arms did not differ significantly, although there was a trend in favor of olanzapine; 29.8% of patients randomized to amisulpride dropped out (n=14) versus 15.2 % (n=7) on olanzapine, a difference of 14.5%, 95%CI -2.5% to 30.7% (p=.093). Patients treated with olanzapine gained significantly more weight than patients treated with amisulpride: 4.40 (SD 3.65) kg versus 2.29 (SD 3.07) kg (P=.021). Otherwise, the two treatment arms did not differ on the incidence of side effects, corrected for phase II baseline assessments.

Phase III (12-week open clozapine)

Of the 40 phase II non-remitters, 12 patients (30.0%) decided not to continue into the 12-week open label phase III for various reasons (refer to Figure 2). A further ten patients dropped out during phase III (drop-out rate during phase III 35.7%), leaving a total of 18 patients who completed the clozapine treatment. Five patients met remission criteria, resulting in a remission rate of 27.8% among those who completed treatment. Within the IIT sample (which classified dropouts as not meeting remission criteria), the remission rate was 17.9%;

Despite the relatively low remission rate, patients demonstrated symptom improvement during clozapine treatment, as shown in Figure 6. The phase III completers improved a total of 24.9 points on the PANSS score relative to study baseline (visit 2: p<.001) and 18.4 points relative to the phase III baseline (at week ten: p=.002). The mean dose of clozapine at the end of Phase III was 279.0 mg/day (SD 130.2); remitters 280.0 mg/day (SD 115.1), non remitters 317.3 (SD 146.7; p=.62). Clozapine blood concentration was assessed at the end of phase III. Remitters (n=5) had a mean clozapine blood concentration of 321 ng/ml (SD 226), non-remitters (n=13) had a mean clozapine concentration of 350 ng/ml (SD 391).

Phase I-III

Out of the 446 patient who initiated the first treatment phase, a total of 287 patients met remission criteria at one of the three treatment phases, adding up to an overall remission rate of 64.3% after a maximum of 20 treatment weeks. The cumulative remission rate based on the completers of the three phases was 76.4%. Figure 6 shows a steady decline in the mean total PANSS scores over the course of each individual treatment phase. In supplemental Figure 1, the Kaplan-Meier curve for dropout over time is depicted. After 20 week of follow-up, the proportion still under study, censoring for remission, was still 0.651.

The mean doses of amisulpride, olanzapine and clozapine in the three treatment phases are included in Table 2; for drop outs, the dose at the last visit has been used. The use of concomitant medication in each phase is shown in Table 3.

Sexual dysfunction and extrapyramidal symptoms are reported in Table 4. Weight changes included in Table 4 are relative to the baseline of the corresponding study phase. An extensive report of all side effects reported is provided in a table in the appendix. The incidence of Serious Adverse Events did not differ between the treatment arms in phase II: one patient randomized to olanzapine was hospitalized due to an epileptic seizure, and one patient randomized to amisulpride was hospitalized twice during phase II due to exacerbations of psychotic symptoms. Over the course of the trial, two serious suicide attempts were reported. One resulted in the only death during the trial, seven days after discontinuing amisulpride. The other attempt was during amisulpride treatment in phase I.

48-week follow-up visit

For patients who did not meet remission criteria after completion of phase III, a follow-up visit was scheduled, 48 weeks post- baseline (26 weeks after the final phase III visit). Out of the 11 non-remitters at the end of phase III, 8 patients returned for this visit. The mean total PANSS score was 70.5 (SD 22.3), ranging from 40 to 104. Three patients met remission criteria during this visit. None of the patients were rehospitalised since the end of phase III.

74-week follow-up visit

For all patients who entered phase I, a follow-up visit was scheduled 74 weeks post-baseline. This visit was conducted for 167 patients. The diagnosis at that time point was established: 13 patients (7.8%) were diagnosed with schizophreniform disorder, 22 patients (13.2%) with schizoaffective disorder, 123 patients (73.7%) with schizophrenia and 9 patients (5.3%) received other diagnoses (e.g. psychosis NOS, bipolar disorder, unspecified non-organic psychosis). PANSS data was available for 140 patients; the mean total PANSS score was 50.2 (SD 15.0, range 30-105). 95 patients (56.9%) met remission criteria. Seventeen out of 140 patients (10.2%) were hospitalized at least once since the most recent study visit.

Discussion

Our first major finding is that switching from amisulpride to olanzapine in first-episode schizophrenia did not improve clinical outcome. In fact, of the 93 patients who were randomized an almost equal proportion (45%) achieved remission whether they continued treatment with amisulpride or were switched to olanzapine. Moreover, the clinical outcome in the two groups was also similar when this was defined in terms of symptomatic improvement (as a continuous variable). Extrapolating, these data suggest that if a patient fails to achieve remission on their first antipsychotic drug, switching to a different drug is no more effective than remaining on the same medication and waiting to see if remission is achieved at a later stage.

To our knowledge, this is the first study to examine the effects of switching antipsychotics in patients with (first-episode) schizophrenia who do not respond to their initial antipsychotic treatment (response has been defined differently in the various studies; we used remission in the current study). With the exception of one study, all previous studies were conducted in the later, chronic, stage of the illness. Moreover, the single study in first-episode schizophrenia did not assess whether switching was more effective than staying on the original treatment (for review see[17]). That study[18] compared risperidone and olanzapine in 287 patients with first-episode schizophrenia in a non-randomized, open design. Response was defined as much improved or better on the CGI. Patients who failed to meet response criteria after four weeks were switched to the other antipsychotic; thus switching versus staying on the first medication was not examined. Clozapine was given when there was no response to both antipsychotics. In that study, 75% of patients met response criteria after four weeks, with more responding to olanzapine (82%) than to risperidone (66%). In the second phase of the study, response rates dropped to 17%, with olanzapine again doing better than risperidone. Important differences compared to the present study were that the first antipsychotic was selected by the treating clinician, the definition of response was less stringent, and switching was open. Moreover, it is unclear whether data were analysed on the basis of completers only or whether an ITT analysis was done.

The only double-blind study that compared switching versus continuation in non-responders was conducted in patients with chronic schizophrenia (age around 42 years). Response in the first two weeks was defined as ≥20% reduction in total PANSS scores. This corresponds to a

lesser degree of clinical improvement than the symptomatic remission criterion used in the present study.[19] Patients who did not respond to a two-week open trial with risperidone (2-6 mg/day) were randomized to either continuing on risperidone or were switched to olanzapine (10-20 mg/day). Switching resulted in a small but significantly greater reduction in total PANSS scores after four weeks.

In the current study, after ten weeks of treatment most of the patients were either in symptomatic remission or had dropped out, leaving only 28 of the initial 446 patients (6.3%) eligible for switching to clozapine. Although only five patients treated with clozapine reached remission, there was still a substantial symptomatic improvement in the sample overall, with an average reduction in total PANSS scores of more than 18 points. These results suggest that providing clozapine early in the treatment of patients with first episode schizophrenia may result in clinical improvement, even if this is short of full symptomatic remission. Moreover, because we only followed patients on clozapine for 12 weeks, and the full treatment response may take several months to materialize, remission rates may have improved further had we followed our patients for longer.[20]

Symptomatic remission rates in our study were high: after only four weeks of (open) treatment with amisulpride, 56% of all 446 patients had reached remission, even when assuming that all drop outs were non-remitters; the remission rate increased to 67% when the analysis was restricted to patients who completed the initial 4-week treatment period. This proportion is impressive for two reasons: first, it corresponds to clinical remission, and not just a numerical reduction of symptoms on a rating scale; second, remission was achieved after only four weeks of treatment. Our results therefore suggest that a majority of patients show a clinically meaningful improvement after only a few weeks of treatment - corroborated by the reduction in the Clinical Global Improvement scale. An additional six weeks of treatment led to more improvement, with a further 45% of patients (in both arms) achieving remission. However, because this was based on a smaller sample (due to the high initial remission rate and the drop out between phases), the total remission rate in completers calculated from baseline at the end of Phase II was 65%. Additional treatment with clozapine increased the cumulative remission rate to 76% - again assuming all drop-outs did not achieve remission. This indicates that for the large majority of patients with first episode of schizophrenia, a rapid and (almost) complete symptomatic recovery can be expected with antipsychotic treatment. The high and rapidly occuring symptomatic response found here is

consistent with results reported in other studies in first episode schizophrenia.[21,22] Nevertheless, some first-episode patients will respond only after continuous treatment lasting up to eight weeks.[23]

The doses of antipsychotics used in the present study are consistent with those generally administered in first episode schizophrenia; amisulpride was given in a mean dose of 591 mg/day, olanzapine 15.6 mg/day and clozapine 279 mg/day (with blood levels a little under 350 ng/L). Critically, the doses in remitters and non-remitters were similar, with those in the non-remitters numerically higher in all phases for all drugs, suggesting that non-remission was not attributable to underdosing. Similarly, although the clozapine dose given was relatively low (280-300 mg/day), blood levels in the non-remitters were adequate (> 350 ng/L), so the low remission rate is unlikely to be related to inadequate dosing. Moreover, the clozapine dose we used was comparable to that given in the first-episode study by Lieberman et. al.[20] where 80% of patients on clozapine reached remission.

Side effects were as expected: amisulpride was associated with extrapyramidal side effects and those related to increased prolactin levels; olanzapine and clozapine induced substantial weight gain, even over the relatively short six and twelve-week periods of treatment, respectively. In phase II, side effects were more prominent in the patients on olanzapine compared to amisulpride: this may have been because those intolerant to amisulpride had dropped out in the earlier phase or had developed tolerance. All drugs were associated with a substantial gain in weight over the course of treatment, although it was most pronounced on olanzapine and clozapine.

The results should be viewed in the context of the study's limitations. First, the sample in the second, randomized phase (II) was relatively modest, comprising 93 patients. This was more the result of the high remission rate in Phase I than the number of dropouts, which was less than 17%. However, remission rates in the amisulpride and olanzapine arms were virtually identical, suggesting a larger sample size may not have changed the results. Second, both the initial treatment with amisulpride and the subsequent one with clozapine were open label. This may have increased the remission rates in both phases. It was felt though, that the initial treatment should be pragmatic, reflecting clinical reality as much as possible, whereas the comparison between two drugs in Phase II needed to be as un-biased as possible and therefore double blind. Third, it could be argued that a comparison between continuation with

amisulpride and switching to clozapine in Phase III would have been of interest; the current design cannot address that question. Indeed, whether clozapine has an added benefit over continuation with amisulpride after ten weeks of its use needs further study. Fourth, it may be argued that a 4-week trial is not sufficiently long to decide whether to switch or not. However, a recent meta-analysis suggests this period is sufficient[24]. Finally, although our results show that a large majority of first-episode schizophrenia patients reaches remission within a few months of treatment, failing to stay in remission remains a major impediment in the treatment of schizophrenia[25.]

Current guidelines recommend that clozapine should be offered to patients who have not responded to treatment with two different antipsychotics. However, if the likelihood of non response to one antipsychotic given for a sufficient length of time is similar to that with two courses of different antipsychotics, it may be feasible to define non-response (operationalized as failure to achieve symptomatic remission) on the basis of a single course of antipsychotic treatment, as long as it is given for long enough. Adopting a simpler treatment algorithm with one course of antipsychotic treatment would allow these patients to be identified earlier and reduce the delay before they can be treated with clozapine.

In summary, our results suggest that switching antipsychotics in minimally treated patients with first-episode schizophrenia does not improve outcome in those who are not in symptomatic remission after their first antipsychotic regimen. Although switching to clozapine early in the treatment did not dramatically improve remission rates, it did result in a substantial improvement in symptoms, albeit that many first-episode patients did not tolerate the side effects associated with its treatment.
Employing an algorithm of treatment with a single antipsychotic for up to ten weeks and subsequent use of clozapine in non-remitters, remission can be achieved within 22 weeks for over three quarters of first-episode patients who complete treatment and for almost two thirds of patients where treatment was initiated. Although these results need to be replicated and broadened (using different antipsychotics), they suggest that achieving remission in the early stages of schizophrenia is possible in the large majority of patients using a simple treatment algorithm of sequential use of amisulpride and clozapine.

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Contributors

RSK, SK, IES, IWR, SL, SH and WWF designed the study. RSK and SK obtained funding. RSK supervised the study. MJCE, RSK and IWR analyzed and interpreted the data. RSK, IWR and MJCE drafted the report. RSK, IWR, SL, PM, SWL, ML, CA, PD, RD, CM, SH, DR, MW, SG, BG, WWF and IES participated in the collection of data. All authors participated in the critical revision of the report and approved the final report.

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Declaration of interests

-René S. Kahn: personal fees for consultancy from Alkermes, Minerva Neuroscience, Gedeon-Richter and Otsuka; personal fees from Otsuka/Lundbeck as speaker

-Inge Winter van Rossum, Paola Dazzan, Philip McGuire, Richard Drake, Dan Rujescu, Mark Weiser, Shitij Kapur, Marion Leboyer have nothing to disclose.

-Stefan Leucht: fees for consulting from LB Pharma, Lundbeck, Otsuka, TEVA and Geodon Richter; fees for lectures from Janssen, Lilly, Lundbeck, Otsuka, SanofiAventis and Servier

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FIGURES: The OPTiMiSE trial: a three-phase, double blind randomised switching study in first episode schizophrenia and schizophreniform disorder comparing amisulpride and olanzapine followed by open treatment with clozapine.

Figure 1: study design

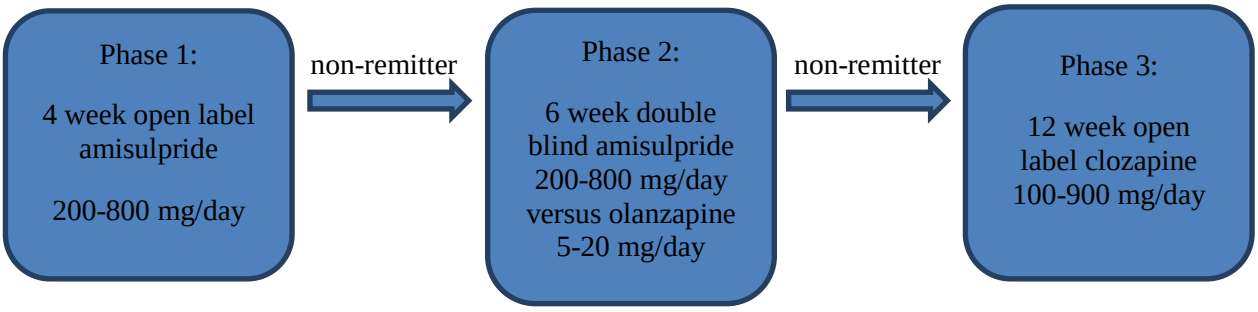
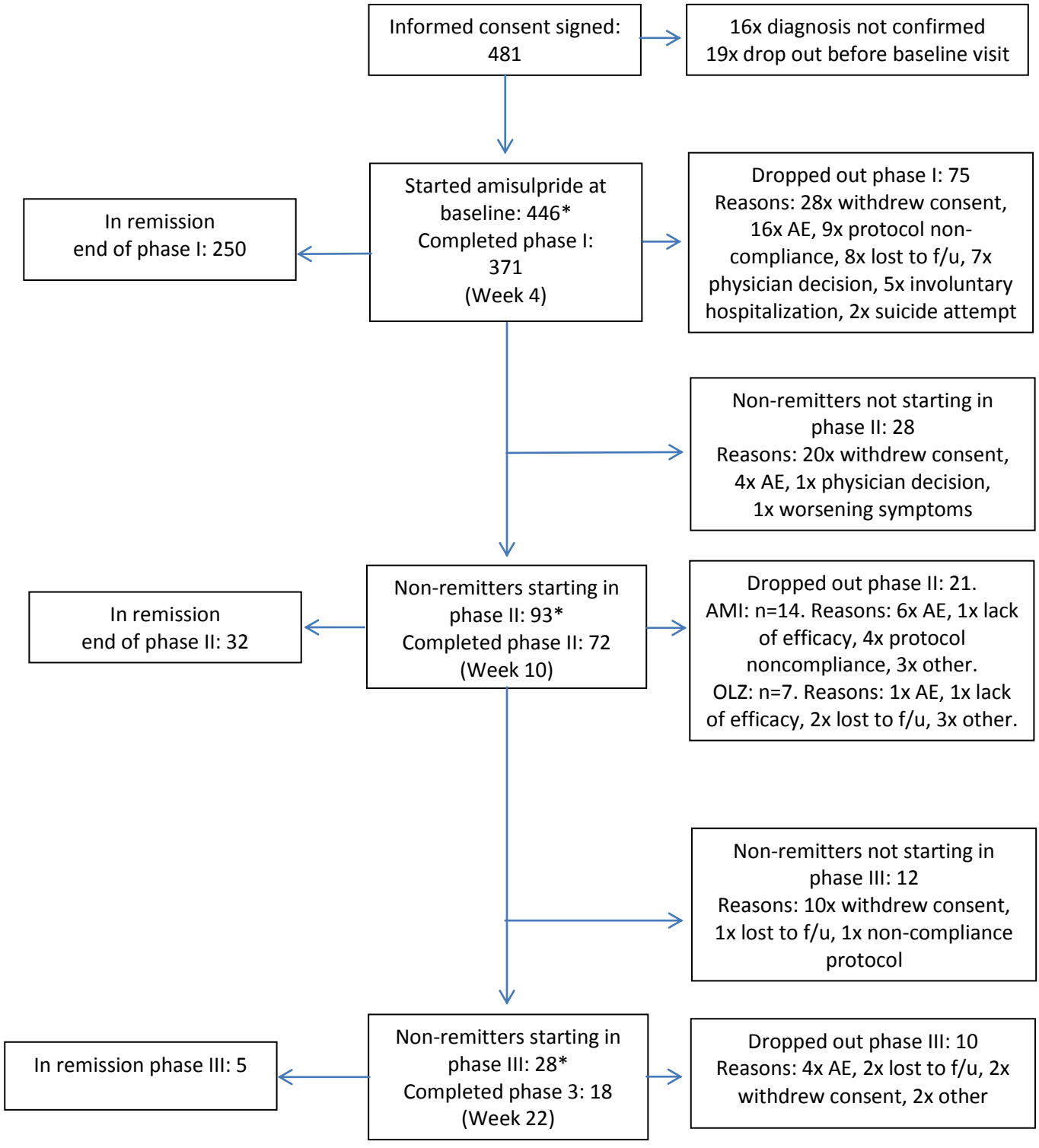
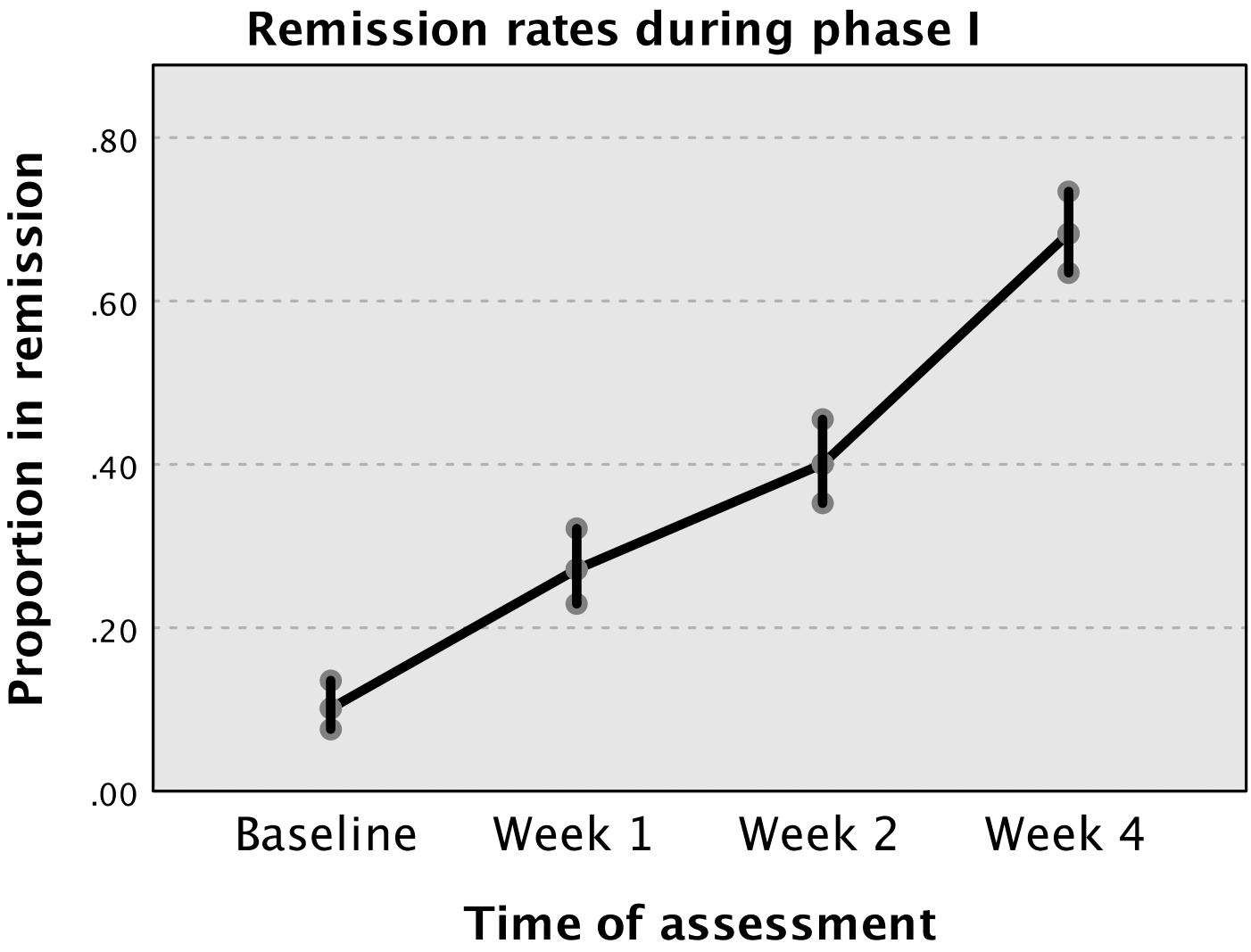


Figure 2: Trial profile

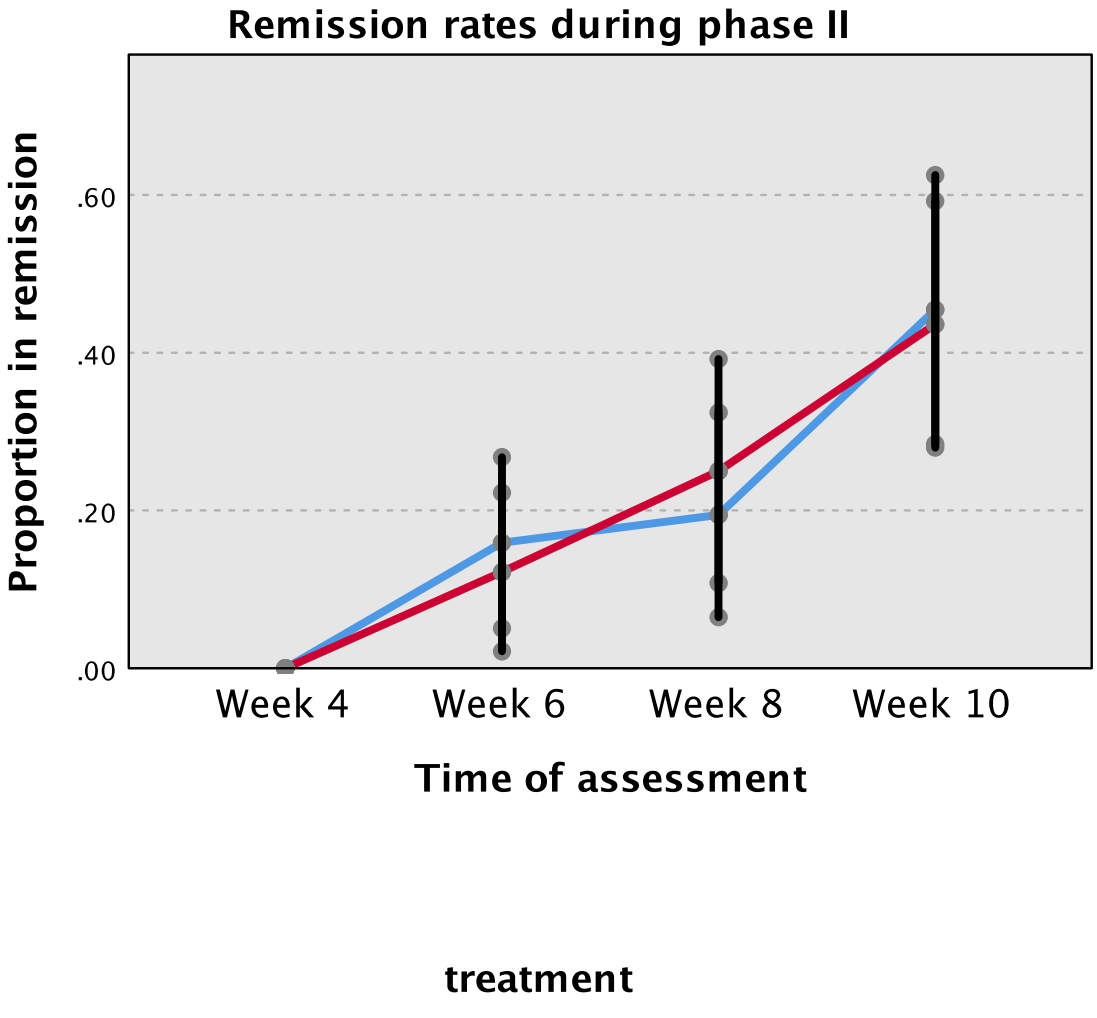


*assessed for primary endpoints

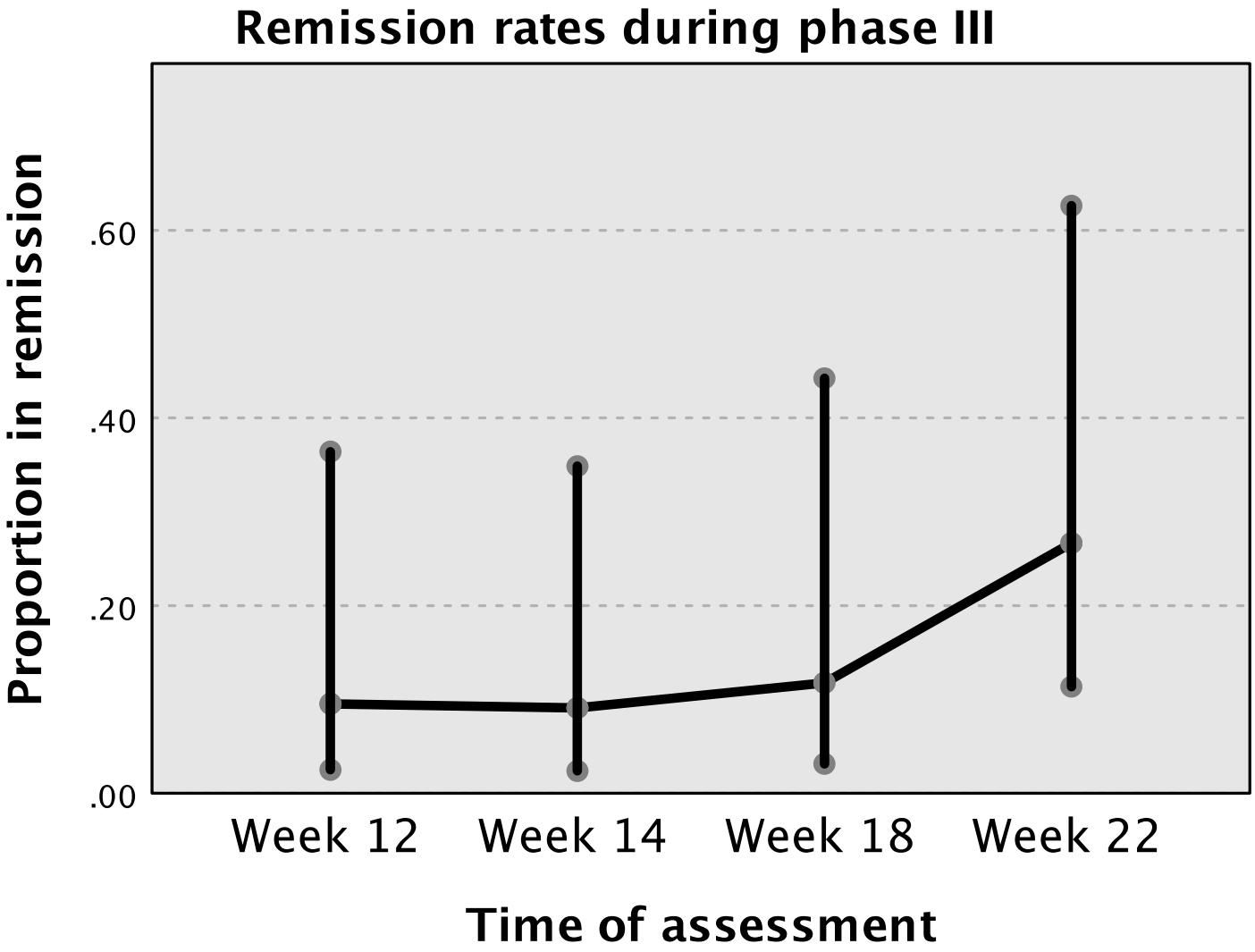
Figure


Remission rates during phase I
Proportion in remission
.80
.60
.40
.20
.00
Baseline
Week 1
Week 2
Week 4
Time of assessment

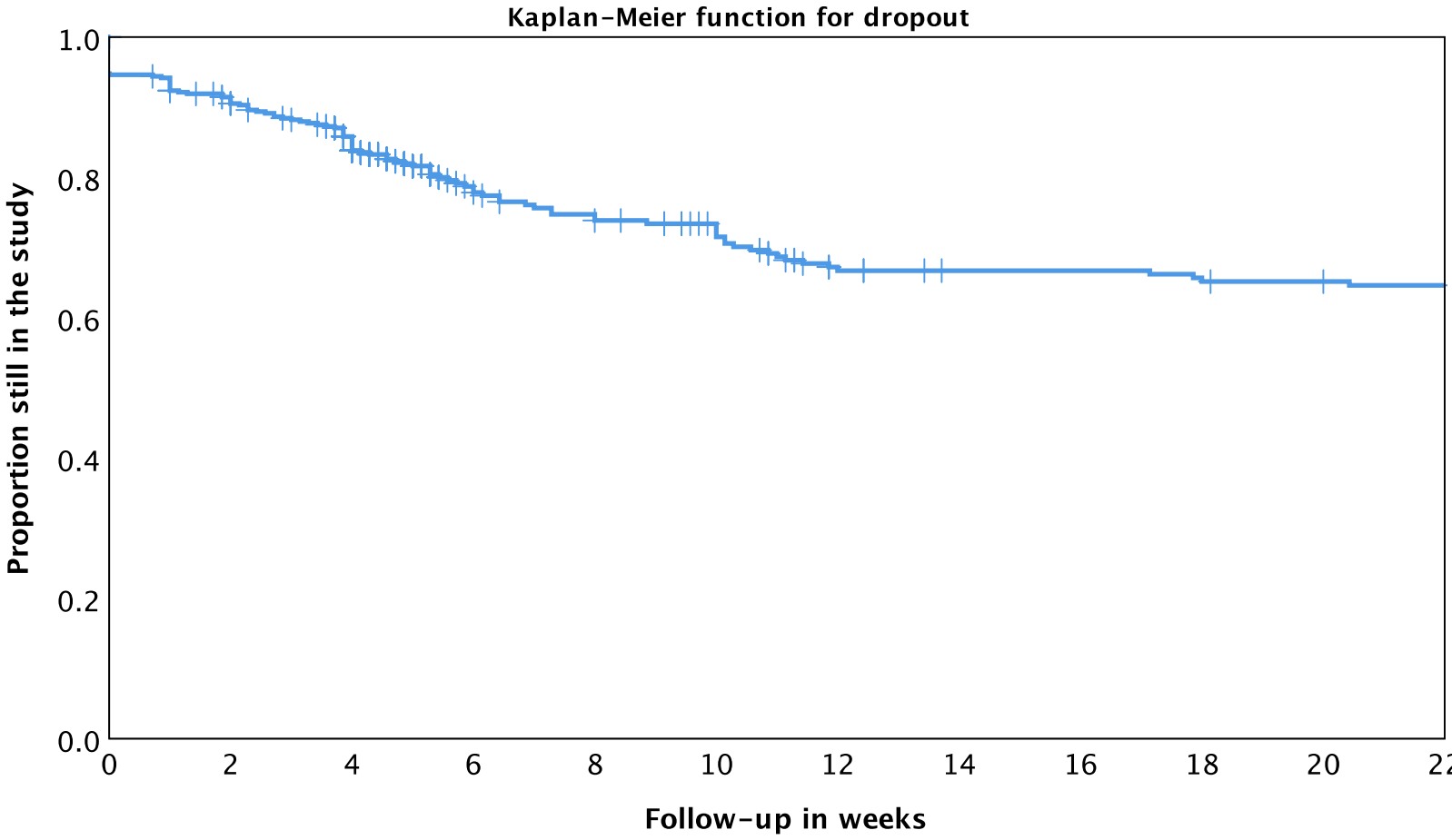
Figure


Remission rates during phase II
Proportion in remission
.60
.40
.20
.00
Week 4
Week 6
Week 8
Week 10
Time of assessment
treatment
Amisulpride
Olanzapine

Figure


Remission rates during phase III
Proportion in remission
.60
.40
.20
.00
Week 12
Week 14
Week 18
Week 22
Time of assessment

Figure


Kaplan-Meier function for dropout
Proportion still in the study
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
14
16
18
20
22
Follow-up in weeks

TABLES: The OPTiMiSE trial: a three-phase, double blind randomized switching study in first episode schizophrenia and schizophreniform disorder comparing amisulpride and olanzapine followed by open treatment with clozapine.

Table 1. Characteristics of patient samples at the start of each treatment phase.

	Start phase I	**Start phase II**	**Start phase III**
Sample size	446	93	28
Age	26.0 (6.0)	25.2 (5.4)	26.3 (6.5)
Women	134/446 (30.0%)	23/93 (24.7%)	7/28 (25.0%)
White	386/446 (86.5%)	86/93 (92.5%)	27/28 (96.4%)
Years of education at baseline*	12.3 (3.0)	11.9 (2.7)	11.4 (2.4)
Living independently at baseline	83/446 (18.6%)	20/93 (21.5%)	8/28 (28.6%)
Employed or student at baseline	185/446 (41.5%)	33/93 (35.5%)	10/28 (35.7%)
Schizophreniform disorder at baseline†	190/446 (42.6%)	28/93 (30.1%)	8/28 (28.6%)
Schizoaffective disorder at baseline†	27/446 (6.1%)	2/93 (2.2%)	2/28 (7.1%)
Schizophrenia at baseline†	229/446 (51.3%)	63/93 (67.7%)	18/28 (64.3%)
Comorbid Major Depressive Disorder at baseline†	34/429 (7.9%)	9/91 (9.7%)	3/28 (10.7%)
Suicidality at baseline†	55/429 (12.8%)	10/91 (11%)	17/28 (17.9%)
Substance abuse and/or dependence in past 12 months at baseline†	75/429 (17.5%)	9/91 (9.9%)	1/28 (3.6%)
Inpatient status at baseline	276/446 (61.9%)	53/93 (57.0%)	17/28 (60.7%)

Duration of untreated psychosis at baseline (months)	6.3 (6.2)	8.4 (7.3)	8.0 (6.5)
Antipsychotic naïve at baseline	187/446 (42.0%)	54/93 (58.1%)	13/28 (46.4%)
PANSS total score§	78.2 (18.7)	85.7 (16.4)	89.0 (16.8)
PANSS Positive Subscale§	20.2 (5.5)	21.7 (5.1)	21.5 (4.6)
PANSS Negative Subscale§	19.4 (7.1)	22.4 (7.0)	23.3 (6.8)
PANSS General Subscale§	38.6 (9.8)	41.6 (9.3)	44.1 (10.1)
CGI Severity¶	4.5 (0.9)	4.7 (0.8)	4.7 (0.9)
Depression score at baseline‡	13.5 (4.6)	14.2 (4.8)	14.6 (4.4)
BMI	23.4 (5.0)	23.9 (4.3)	25.0 (2.6)
Overweight BMI 25 or more	119/436 (26.6%)	25/82 (30.5%)	11/20 (55%)
Abdominal circumference**	83.3 (12.4)	84.1 (10.5)	86.8 (8.5)

Baseline is visit 2, the visit at which study medication is initiated. Data are n/N (%) or mean (SD). Denominators change due to incomplete data. PANSS=Positive and Negative Syndrome Scale. CGI=Clinical Global Impression. BMI=Body Mass Index. *Years in school from 6 years of age onwards. †According to the Mini International Neuropsychiatric Interview 5 plus. Suicidality includes medium to high suicide risk. §Theoretical scores range from 30–210 (total scale), 7–49 (positive scale), 7–49 (negative scale), 16–112 (general psychopathology scale). Higher scores indicate more severe psychopathology. ¶ Theoretical scores range from 1–7; higher scores indicate greater severity of illness. ‡According to the Calgary Depression Scale for Schizophrenia. Theoretical scores range from 0–27; higher scores indicate more depression. ** measured in cm.

Table 2: Mean doses of study medication used during the three phases of the trial

	During phase I Amisulpride	During phase II		During phase III Clozapine
		Amisulpride (n=44)	Olanzapine (n=43)	
Intent To Treat sample	490.4 (207.4)	590.9 (236.1)	15.6 (6.5)	279.0 (130.2)
Completers only	488.0 (203.4)	593.9 (226.3)	16.2 (6.1)	307.0 (137.1)
Drop outs only	511.4 (240.4)	581.8 (275.0)	10.0 (8.2)	207.1 (78.7)

Dosage is indicated in mg per day (SD). Mean dose is based on the dose of each individual patient at the last visit of the applicable phase. For instance, for phase I completers, the dose at visit 5 (end of phase I) is used. For a phase II drop out, the dose at the last visit before dropping out is used.

Table 3: Concomitant medication used during the three phases of the trial

	Baseline (n=446)	**End phase I (n=371)**	**Start phase II (n=93)**	**End phase II (=72)**	**Start phase III (n=28)**	**End phase III (n=18)**
Antidepressants	41 (9.2%)	30 (8.1%)	9 (9.7%)	AMI: 4/33 (12.1%) OLZ: 5/39 (12.8%)	4 (14.3%)	2 (11.1%)
Anxiolytics	111 (24.9%)	61 (16.4%)	22 (23.7%)	AMI: 3/33 (9.1%) OLZ: 9/39 (23.1%)	8 (28.6%)	1 (5.6%)
Mood stabilizers	18 (4.0%)	16 (4.3%)	4 (4.3%)	AMI: 1/33 (3%) OLZ: 2/39 (5.1%)	0	0
Hypnotics	150 (33.4%)	61 (16.4%)	27 (29.0%)	AMI: 5/33 (15.2%) OLZ: 9/39 (23.1%)	8 (28.6%)	1 (5.6%)
Anti-EPS medication	48 (10.8%)	73 (19.7%)	32 (34.4%)	AMI: 6/33 (18.2%) OLZ: 6/39 (15.4%)	6 (21.4%)	1 (5.6%)

Benzodiazepine used to treat anxiety has been coded as ‘anxiolytic’; for all other indications for use, they have been coded as benzodiazepine. Anti-epileptics have been coded as ‘mood stabilizer’ if the indication for use was mood-related, e.g. ‘irritability’ or ‘impulsiveness’. That is, anti-epileptics prescribed for epilepsy were not included in this overview.

Table 4. Symptom severity and side effects per treatment phase.

	End of phase I	End of phase II	End of phase III
PANSS total score change from baseline*	-19.1 (17.9)	AMI: -10.1 (19.9) OLZ: -6.1 (13.9)	-18.4 (21.7)
PANSS Positive Subscale change from baseline *	-7.1 (5.7)	AMI: -2.8 (6.0) OLZ: -1.1 (4.2)	-5.5 (5.8)
PANSS Negative Subscale change from baseline*	-3.2 (5.6)	AMI: -3.7 (6.8) OLZ: -1.8 (5.1)	-4.5 (5.1)
PANSS General Subscale change from baseline *	-8.8 (9.6)	AMI: -3.7 (10.3) OLZ: -3.3 (8.1)	-8.4 (12.2)
CGI Severity change from baseline †	-1.1 (1.1)	AMI: -0.33 (1.1) OLZ: -0.26 (0.9)	Not assessed
Sexual side effects ††			
Male	107/371 (28.8%)	AMI: 2/33 (6.1%) OLZ: 8/39 (20.5%)	6/18 (33.3%)
Female	61/371 (16.4%)	AMI: 5/33 (15.2%) OLZ: 6/39 (15.4%)	3/18 (16.7%)
Extrapyramidal symptoms††			
Dystonia	58/371 (15.6%)	AMI: 1/33 (3.0%) OLZ: 4/39 (10.3%)	3/18 (16.7%)
Rigidity	83/371 (22.4%)	AMI: 3/33 (9.1%) OLZ: 9/39 (23.1%)	4/18 (22.2%)
Tremor	92/371 (24.8%)	AMI: 3/33 (9.1%) OLZ: 10/39	3/18 (16.7%)
Akathisia	105/371 (28.3%)	AMI: 1/33 (3.0%) OLZ: 5/39 (12.8%)	0/18 (0%)
Weight change from	2.5 (4.0)	AMI: 2.7 (2.9)	4.8 (5.5)

baseline		OLZ: 4.2 (3.6)	
Weight gain 7% or more from baseline	70/371 (18.9%)	AMI: 5/33 (15.2%) OLZ: 10/39 (25.6%)	8/18 (44.4%)
Abdominal circumference change from baseline**	2.1 (4.7)	AMI: 1.4 (2.7) OLZ: 4.2 (5.0)	3.5 (5.9)

Baseline for phase I is visit 2, the visit at which study medication is initiated. Baseline for phases II and III are the first visits of these respective phases, that is, visit 5 for phase II and visit 8 for phase III. Data are n/N (%) or mean (SD). Denominators change due to incomplete data. PANSS=Positive and Negative Syndrome Scale. CGI=Clinical Global Impression. AMI=amisulpride. OLZ= olanzapine. *Theoretical scores range from 30–210 (total scale), 7–49 (positive scale), 7–49 (negative scale), 16–112 (general psychopathology scale). Higher scores indicate more severe psychopathology. † Theoretical scores range from 1–7; higher scores indicate greater severity of illness. ††Any symptoms scored on the Udvalg for Kliniske Undersøgelser questionnaire during the respective phase: for men: increased/decreased libido, orgastic dysfunction, gynaecomastia, or erectile/ejaculatory dysfunction (six items); for women: increased/decreased libido, orgastic dysfunction, menorrhagia, amenorrhoea, galactorrhoea, or dry vagina (seven items); an extensive list of adverse events is reported in the appendix. ** measured in centimeters.

Table 5. Baseline characteristics of patients included in phase II, according to randomized treatment group

	Amisulpride	Olanzapine
Sample size	47	46
Age (years)	24.9 (5.4)	24.6 (5.5)
Women	11 (23.4%)	12 (26.1%)
White	43 (91.5%)	43 (93.5%)
Years of education at baseline*	12.4 (2.9)	11.4 (2.3)
Living independently at baseline	11 (23.4%)	9 (19.6%)
Employed or student at baseline	17 (36.2%)	16 (34.8%)
Schizophreniform disorder at baseline†	15 (31.9%)	14 (30.4%)
Schizoaffective disorder at baseline†	1 (2.1%)	2 (4.3%)
Schizophrenia at baseline†	35 (74.5%)	30 (65.2%)
Comorbid Major Depressive Disorder at baseline†	5 (10.9%)	4 (8.9%)
Suicidality at baseline†	6 (11.0%)	8 (17.8%)
Substance abuse and/or dependence in past 12 months at baseline†	1 (2.2%)	2 (4.4%)
Inpatient status at baseline	27 (57.4%)	26 (56.5%)
Duration of untreated psychosis at baseline (months)	9.5 (7.8)	7.2 (6.6)
PANSS total score§	79.1 (16.2)	75.2 (16.2)
PANSS Positive Subscale§	18.2 (5.1)	17.0 (5.1)
PANSS Negative Subscale§	22.5 (6.8)	20.9 (6.5)
PANSS General Subscale§	38.4 (9.1)	37.2 (9.4)

Baseline is visit 2, the visit at which study medication is initiated, except for the PANSS scores. Data are n (%) or mean (SD). PANSS=Positive and Negative Syndrome Scale.

*Years in school from 6 years of age onwards. †According to the Mini International Neuropsychiatric Interview 5 plus. Suicidality includes medium to high suicide risk. §Theoretical scores range from 30–210 (total scale), 7–49 (positive scale), 7–49 (negative scale), 16–112 (general psychopathology scale). Higher scores indicate more severe psychopathology.

Table

Appendix to 'The OPTiMiSE trial: a three-phase, double blind randomised switching study in first episode schizophrenia and schizophreniform disorder comparing amisulpride and olanzapine followed by open treatment with clozapine'

Appendix 1: all adverse effects reported through the UKU scale

Adverse effect	End of phase I	End of phase II	End of phase III
Concentration difficulties	118/371 (31.8%)	AMI: 10/33 (30.3%) OLZ: 15/39 (38.5%)	3/18 (16.7%)
Asthenia/Lassitude/Increased Fatigability	156/371 (42.0%)	AMI: 8/33 (24.2%) OLZ: 14/39 (35.9%)	3/18 (16.7%)
Sleepiness/Sedation	156/371 (42.0%)	AMI: 10/33 (30.3%) OLZ: 21/39 (53.8%)	6/18 (33.3%)
Failing memory	76/371 (20.5%)	AMI: 3/33 (9.1%) OLZ: 10/39 (25.6%)	0/18 (0%)
Depression	98/371 (26.4%)	AMI: 8/33 (24.2%) OLZ: 15/39 (38.5%)	2/18 (11.1%)
Tension/Inner unrest	112/371 (30.2%)	AMI: 7/33 (21.2%) OLZ: 13/39 (33.3%)	2/18 (11.1%)
Increased duration of sleep	105/371 (28.3%)	AMI: 10/33 (30.3%) OLZ: 19/39 (48.7%)	4/18 (22.2%)
Reduced duration of sleep	36/371 (9.7%)	AMI: 2/33 (6.1%) OLZ: 1/39 (2.6%)	0/18 (0%)
Increased dream activity	80/371 (21.6%)	AMI: 5/33 (15.2%) OLZ: 7/39 (17.9%)	1/18 (5.6%)
Emotional indifference	88/371 (23.7%)	AMI: 8/33 (24.2%) OLZ: 10/39 (25.6%)	3/18 (16.7%)
Epileptic seizures	3/371 (0.8%)	AMI: 1/33 (3.0%) OLZ: 1/39 (2.6%)	0/18 (0%)
Paraesthesias	21/371 (5.7%)	AMI: 1/33 (3.0%) OLZ: 6/39 (15.4%)	0/18 (0%)

Accommodation disturbances	25/371 (6.7%)	AMI: 1/33 (3.0%) OLZ: 3/39 (7.7%)	2/18 (11.1%)
Increased salivation	56/371 (15.1%)	AMI: 4/33 (12.1%) OLZ: 7/39 (17.9%)	6/18 (33.3%)
Reduced salivation	30/371 (8.1%)	AMI: 1/33 (3.0%) OLZ: 7/39 (17.9%)	1/18 (5.6%)
Nausea/Vomiting	15/371 (4.0%)	AMI: 1/33 (3.0%) OLZ: 4/39 (10.3%)	1/18 (5.6%)
Diarrhoea	16/371 (4.3%)	AMI: 1/33 (3.0%) OLZ: 5/39 (12.8%)	0/18 (0%)
Constipation	41/371 (11.1%)	AMI: 2/33 (6.1%) OLZ: 2/39 (5.1%)	2/18 (11.1%)
Micturition disturbances	17/371 (4.6%)	AMI: 0/33 (0%) OLZ: 2/39 (5.1%)	0/18 (0%)
Polyuria/Polydipsia	39/371 (10.5%)	AMI: 2/33 (6.1%) OLZ: 2/39 (5.1%)	1/18 (5.6%)
Orthostatic dizziness	42/371 (11.3%)	AMI: 0/33 (0%) OLZ: 9/39 (23.1%)	2/18 (11.1%)
Palpitations/Tachycardia	32/371 (8.6%)	AMI: 1/33 (3.0%) OLZ: 7/39 (17.9%)	3/18 (16.7%)
Increased tendency to sweating	31/371 (8.4%)	AMI: 2/33 (6.1%) OLZ: 4/39 (10.3%)	0/18 (0%)
Rash – morbiliform	1/371 (0.3%)	AMI: 0/33 (0%) OLZ: 1/39 (2.6%)	0/18 (0%)
Rash - petechial	0/371 (0%)	AMI: 0/33 (0%) OLZ: 1/39 (2.6%)	0/18 (0%)
Rash – urticarial	2/371 (0.5%)	AMI: 1/33 (3.0%) OLZ: 0/39 (0%)	1/18 (5.6%)
Rash - psoriatic	0/371 (0%)	AMI: 0/33 (0%) OLZ: 0/39 (0%)	0/18 (0%)
Pruritus	23/371 (6.2%)	AMI: 1/33 (3.0%)	0/18 (0%)

		OLZ: 1/39 (2.6%)	
Photosensitivity	16/371 (4.3%)	AMI: 1/33 (3.0%) OLZ: 1/39 (2.6%)	1/18 (5.6%)
Increased pigmentation	1/371 (0.3%)	AMI: 0/33 (0%) OLZ: 0/39 (0%)	0/18 (0%)
Headache – tension headache	39/371 (10.5%)	AMI: 1/33 (3.0%) OLZ: 2/39 (5.1%)	0/18 (0%)
Headache – migraine	2/371 (0.5%)	AMI: 0/33 (0%) OLZ: 1/39 (2.6%)	0/18 (0%)
Headache – other forms	13/371 (3.5%)	AMI: 0/33 (0%) OLZ: 1/39 (2.6%)	1/18 (5.6%)
Physical dependence	5/371 (1.3%)	AMI: 0/33 (0%) OLZ: 0/39 (0%)	0/18 (0%)
Psychic dependence	14/371 (3.7%)	AMI: 0/33 (0%) OLZ: 1/39 (2.6%)	0/18 (0%)

Appendix 2: OPTiMiSE (OPtimization of Treatment and Management of Schizophrenia in Europe) Study Group

Principal Investigator / Sponsor: R S Kahn.

Study Management Group: R S Kahn, I E Sommer (trial coordinator until end of 2012), I Winter van Rossum (trial coordinator since end of 2012), M Somers, P C Ywema.

Executive Board: R S Kahn, S Kapur, P McGuire, M Leboyer, A Meyer-Lindenberg, S Lewis, S Leucht, B Glenthoj, C Arango, W W Fleischhacker.

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Clinical Research Associates: A L Meijering, J Petter, R van de Brug.

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Participating investigators (CC=country coordinator; SC=site coordinator),

centres, and countries:

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Bulgaria—L G Hranov (CC), V Hranov (SC);

Czech Republic: J Libiger (CC), R Köhler (SC Hradec Králové), P Mohr (SC Prague);

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UK: P Dazzan (CC), R Perez-Iglesias (SC KC London), S Lewis (SC Manchester), R Drake (SC Manchester), S Gregory (SC WLMHT London), D Wilson (SC WLMHT London).

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Appendix 4: Protocol amendments, following the original protocol dated 05-11-2010

Amendment 1 - 30-03-2011:

- follow-up visits at 48 weeks (remission criteria assessment, for phase III non-remitters only) and 72 (remission criteria assessment) were added to enable long term follow-up of participants.
- contraceptive use as inclusion criteria was added on request of regulatory authorities.
- inclusion criteria regarding the onset of illness was changed from 'a maximum of 2 years since onset of positive symptoms' to 'a maximum of 2 years since onset of psychosis'. Many patients have experienced vague symptoms in their childhood, but the onset of psychosis was regarded a more relevant starting point.
- For patients using clozapine, leucocyte checks need to be continued for at least 4 weeks when a patient discontinues clozapine.
- Several reasons for withdrawal of participants were added: 1) The nature of the patients treatment is changed to coercive treatment (based on judicial ruling); 2) In contrast to the patient's status at enrollment, the patient is now represented by a legal guardian or under legal custody; 3) Emergence of one or more contraindications against any of the study drugs as mentioned in the Summaries of Product Characteristics (refer to Appendix B). In particular, clozapine use needs to be discontinued when one or more of the following adverse events occur: severe leucopenia (leucocyte count $<3000/mm^3$ or $3.0x10^9/l$) or neutropenia (count $<1500/mm^3$ or $1.5x10^9/l$), myocarditis or cardiac arrhythmias; 4) Patient becomes pregnant or initiates lactation

Amendment 2 – 01-07-2011:

- the recommended tapering schedule of study medication was adjusted to slow down the dose increase in order to decrease the chance on and severity of extrapyramidal symptoms, as the first patient who entered the study suffered from severe EPS.
- on request of the participating centers, a titration recommendation for the transfer from phase I to phase II, and from phase II to phase III study medication was included.
- target dose of 400 mg/day amisulpride was added, in line with findings from the EUFEST study. However, clinicians could deviate from the target dose as well as the titration scheme if deemed necessary.

Amendment 3 – 04-07-2012:

- the eligibility for entering the Psychosocial Intervention component after the pharmaco-therapeutic component was no longer limited to patients meeting remission criteria, but also for drop outs and patients not meeting remission criteria, as they could also benefit from this intervention.
- It was found that 'Schizophreniform disorder' could not be completely assessed through the M.I.N.I. diagnostic interview. Therefore the confirmation of this diagnosis was rephrased as follows: Schizophreniform disorder is assessed through a M.I.N.I. diagnosis of psychosis NOS complemented by a diagnosis of schizophreniform disorder according to DSM-IV criteria.
- a clinical diagnosis was added to the long term f/u visit 22 (74 weeks) to gain insight into the stability of the diagnosis of participants at baseline.

Amendment 4 – 15-11-2013:

- closure of one participating center, addition of a new participating center.
- increase of patient sample from 350 to 500, due to the high remission rate in phase I.
- a third MRS scan was added, 10 weeks after baseline, providing a longer term follow up of the timing of any glutamate changes, and investigating any differential effects of amisulpride versus olanzapine on glutamate changes.
- changes in Serious Adverse Event reporting were implemented: 1) pregnancy is no longer reported as SAE but rather an AE; 2) hospitalisation due to psychiatric exacerbation is reported only in the annual line listings, due to the high frequency of occurrence at this early stage of the illness and the fact that immediate reporting does not have added value.

Amendment 5 – 07-05-2015:

- recalculation of power analyses for MRS.
- following changes in the amisulpride SPC, a safety procedure was added: if female patients have a history of breast cancer, and/or a first degree relative with a (history of) breast cancer, prolactin levels should be assessed at the local lab, at visit 2 and visit 5.
- a blood count assessment was added to the biomarker blood draws, in order to support epigenetic analyses.

Amendment 6 – 06-07-2015:

The generic amisulpride used for the study thus far, was no longer commercially available, therefore a switch to another generic amisulpride was required.

Table

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6-7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Appendix
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 2
	13b	For each group, losses and exclusions after randomisation, together with reasons	10-12 and Figure 2
Recruitment	14a	Dates defining the periods of recruitment and follow-up	10
	14b	Why the trial ended or was stopped	10
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10-13 and Tables 2-4
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10-13 and Tables 2-4
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	11
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12-13, table 4 and appendix
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14-18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	15-18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-18
Other information			
Registration	23	Registration number and name of trial registry	3 & 6
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	4 & 9

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Optimization of Treatment and Management of Schizophrenia in Europe

version 2.4, dated July 6, 2015

Study protocol

(overall protocol of WP 1, 2, 3 and 5)

EudraCT-Number: 2010-020185-19

Protocol-Code-Number: KP7 242114

PROTOCOL TITLE 'Optimization of Treatment and Management of Schizophrenia in Europe'

Protocol ID	KP7 242114
Short title	The OPTiMiSE trial
Version	2.4
Date	July 6, 2015
Coordinating investigator/project leader	Prof. Dr. René S Kahn
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Index of contents

SUMMARY

Rationale:

This study will focus on two goals: optimising current treatments in schizophrenia and explore novel therapeutic options for schizophrenia. The study intends to both address basic, but so far unanswered, questions in the treatment of schizophrenia and develop new interventions. It is expected that the project will lead to evidence that is directly applicable to treatment guidelines, and will identify potential mechanisms for new drug development.

Objectives:

I To test applicability of amisulpride as the first step in a treatment algorithm.
II To test guideline recommendation that non-responders to an antipsychotic drug benefit from a switch to an antipsychotic with a different receptor binding profile.
III To provide the acceptability and outcome data on the application of clozapine in non-responding patients within the first 10 weeks of their treatment initiation.
IV To test if an IT-enabled psychosocial intervention can improve treatment adherence and global functional outcome in symptomatically remitted first-episode schizophrenia patients.
V To test whether glutamatergic markers predict response to first and second line treatments.
VI To test if a combination of pharmacogenetic, proteomics- and metabolomic markers can provide clinical valuable predictive value.
VII To define the nature and prevalence of 'organic' pathology in patients presenting with a first episode schizophreniform psychosis
VIII To determine the extent to which MRI measures at first presentation predict the therapeutic response to subsequent antipsychotic treatment.

Study design:

Intervention study consisting of: medication intervention part (partly randomized, controlled, double-blind), psychosocial intervention part (randomized, controlled), MRI part.

Study population:

500 first episode schizophrenia patients, aged 18-40 years, will be included at multiple (18-30) sites. Patients can only be included if they have used less than 2 weeks of antipsychotic medication in the year prior to inclusion and/or 6 weeks lifetime.

Intervention:

MRI part: At screening an MRI scan will be made to screen for neurological pathology. Venous blood will be obtained for genetic and metabolic analyses. The MRI and blood values obtained at screening and baseline will be used to predict treatment response.
Medication part: All patients will be provided open-label amisulpride for four weeks (phase I). Non-responders will enter the double blind phase of the study (phase II). In a randomized fashion, non-responders will either continue on amisulpride or switch to

olanzapine for six weeks. Patients who have still not responded will be prescribed clozapine open-label for twelve weeks (phase III).
Psychosocial part: All patients who respond, either after four weeks, after ten weeks or on clozapine will be randomized to a psychosocial intervention (twelve weeks) or to treatment as usual. Patients who did not respond but do wish to participate in this study component may also be randomized. The psychosocial intervention consists of psychoeducation, motivational interviewing and SMS warnings to improve medication adherence. The medication that is prescribed during this phase is the choice of the patient and physician.

Main study parameters/endpoints:

The primary outcome for the medication part is the number of participants in remission at the end of phase I, II and III.
The primary outcomes for the psychosocial intervention are drug adherence rates defined categorically (adherent vs non-adherent) as a function of standardised self report measured through the Sellwood rating scale and Kemp rating scales; and global functioning at 1 year.
The primary outcome for the MRI screening is the percentage first episode patients that show radiological abnormalities suggestive of neurological disorders.
The primary outcome for the biological predictors is the percentage of non-responders that show biological variations compared with the responders (eg: genetic variants).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
Use of the study drugs will imply that there is a risk of side effects, as all anti-psychotic drugs carry the risk of side-effects. In addition, participation in this study will take more time than regular treatment, because of the standardised interviews that will be done. The risks and discomfort of blood samples are the same as always if blood is drawn from a vein. Minor injuries and irritations can occur. In rare cases a local infection can occur. The MRI scan procedure is painless and safe and there are no known health risks.

1. Introduction and aims

Despite nearly fifty years of pharmacological and psychosocial research, the overall prognosis of schizophrenia has improved only marginally. While the efficacy of most antipsychotic medication is generally uncontested, their overall functional impact has been modest. This disappointing fact may be attributable to three major issues: first, a considerable minority of patients still does not respond sufficiently to current treatments; second, patients who do respond to medication often discontinue it and relapse; finally, even patients who *do* respond well to treatment and *do* adhere to it, continue to suffer from substantial cognitive and functional deficits severely limiting their potential.In order to improve this unsatisfactory result, this study aims to optimize current treatments in schizophrenia and explore novel therapeutic options for schizophrenia. The study comprises a medication intervention part, a psychosocial intervention part, a biological predictor part and an MRI part.

1.1 Medication intervention: Finding evidence for pharmacotherapy guidelines in first episode schizophrenia

While effective antipsychotic treatments are available for nearly fifty years – the application and implementation of these treatments is far from optimal. There are a number of elementary questions in the treatment of schizophrenia that need to be answered. When a psychiatrist is faced with a new patient with schizophrenia he will no doubt use an antipsychotic to start treatment; however, he has little guidance on some very simple and fundamental questions. Is there a rational basis for choosing the first antipsychotic? Can I predict how well the patient will do? When the patient fails to respond to the first antipsychotic how long do I wait? Do I continue for some more time or do I switch to another antipsychotic? If so, which one?
Once it has been decided that antipsychotic treatment is to be initiated the question arises how to prioritize the currently available treatments in a rational and optimal manner. While there are several ‘treatment’ algorithms for schizophrenia, all of them are agnostic as to the choice of the first antipsychotic (so long as it is not a depot or clozapine). In essence, all currently available antipsychotics are considered equal, even though we know they differ in mechanism of action. Although numerous national treatment guidelines for schizophrenia are available, recommendations for choice of drug (or switching in case of non-response) are usually vague. A case can be made that a drug which is cheap, widely available, and has the simplest and most specific known mechanism should be tried first. This drug is amisulpride – it is a specific D2 blocker, has atypical properties, is as effective as any of the other atypicals, has a benign profile on metabolic parameters and in the recently completed EUFEST trial of first episode patients showed the best rate of remission (40% after 4 weeks of treatment).
Aim: to test the widespread application, patient-acceptability and outcomes of amisulpride as the first step in the treatment of 500 patients with a first episode of schizophrenia.

No one treatment will be adequate for all patients. Prospective, sequential studies are necessary to develop treatment algorithms for schizophrenia, but these are almost completely missing. While every year hundreds of studies on schizophrenia are published (the register of the Cochrane Schizophrenia Group currently includes 12000 controlled clinical trials), most of the studies focus on the question whether a

specific drug or psychotherapeutic intervention works or not. What is, however, lacking are mechanism-based, rational, sequential studies that address how to deal with treatment non-response. Evidence is absent as to what the most appropriate follow-up actions should be: continue treatment, or switch to another antipsychotic (with another mechanism of action). The use of amisulpride as the first treatment has another benefit – it provides a rationale for the kind of drug that should be tried next. Amisulpride is a specific D2/3 blocker and thus differs from the other atypicals, which have multi-receptor blocking properties. While at a group level, it has been hard to show convincingly that one drug is superior to another; there may still be empirical support for a rational sequential strategy. Thus, for patients who do not show remission to amisulpride, we will compare the option of additional time on the same mechanism (the stay option) or moving to a drug with a widely different mechanism of action (the switch option).

Aim: to provide the first randomised double-blind trial comparing a mechanistically based stay-or-switch algorithm as the second step in the treatment of schizophrenia.

The unfortunate reality of schizophrenia is that despite all interventions and approaches, there is a small percentage of patients, who do not respond to first, or even second line treatments. The treatment algorithms are quite explicit about what to do next – switch to clozapine. This is one intervention that is best supported by evidence. However, in this instance there is a great gap between algorithms and reality. According to all treatment algorithms, if patients fail 6 weeks each for two antipsychotics at adequate doses they should be offered clozapine. This means that a first episode patient should be offered clozapine within 12 weeks of start of treatment. However, standard treatment evidence shows that the average patient being initiated on clozapine has often been psychotic for nearly 10-12 years. In a recent small trial, the first episode team in Toronto showed that clozapine can be systematically applied as the third line treatment within the first 6 months, and shows dramatic benefits for those who had failed two other atypical medications (Agid et al. 2007). Clearly then, theory and initial evidence suggest that clozapine should be used early, not as a last resort. While one does not need another randomized trial to demonstrate the superiority of clozapine yet again – one does need a large scale demonstration of its early application and its superior impact on outcomes.

Aim: to provide the acceptability and outcome data on the first systematic, large-scale, application of clozapine in non-responding patients within the first 10 weeks of their treatment initiation.

1.2 Psychosocial intervention: Finding interventions to improve medication adherence

Fortunately, first episode patients do often respond reasonably well; the main challenge then becomes how to keep them well. The single best predictor of continued wellness for the patient is compliance with treatment. And while every psychiatrist knows this to be the case – there are few, if any, simple, effective and widely applicable manoeuvres at their disposal to increase compliance.

The sad fact remains that more than half of these patients will stop their medications and the majority of them will relapse over the first year. Maintaining drug treatment will reduce risk of relapse by five fold – so the challenge is how to keep these patients on the medication to which they have responded well. While a number of

adherence interventions have been shown to have effect – most of them have been cumbersome, site-specific, and difficult to disseminate broadly. To be clinically relevant, we need individually-tailored yet widely applicable psychosocial interventions that incorporate elements that have been shown to be effective in previous studies. Several important elements in non adherence can be identified: lack of insight in mental illness, negative attitude to medication, no perceived benefits, and lack of support from family members, perceived side effects and forgetfulness. To address these, we have developed an IT-enabled programme comprising three elements: web-based psycho-education; a web-enabled personally-delivered motivational intervention package; and electronic medication alerts and updates. As these elements of non-adherence may be especially present in patients who do not remit, we cannot justify excluding those non-remitted patients who wish to take part in this study component.

Aim: to provide a controlled and randomized test of an IT-enabled, widely applicable, intervention to improve treatment adherence and measure its effects on adherence, symptoms and global functional outcome in first-episode schizophrenia patients.

1.3 Finding biological predictors of treatment response

While we expect that the objectives above will lead to greater clarity and effectiveness in the use of current treatments – there is no denying that even when our current medications work well and induce symptomatic remission, most patients with schizophrenia remain incapacitated. Two major problems linger – residual positive symptoms for a sizeable minority; residual cognitive and negative symptoms, for a sizeable majority. Five decades of D2-antispychotic research has failed to make a major improvement on these aspects of the illness. Thus, we need novel mechanisms and novel concepts. Part of the study will focus on the development of new treatments using agents that are already available and make use of translational studies using genetics/genomics and neurochemical imaging to identify new pathways for drug development. We intend to use genetic and genomic approaches to explore the possibility of segmenting patient groups and identifying new pathways for future drug development. We expect this component of the study to provide important novel leads for the development of new treatments in schizophrenia, especially for those aspects of the illness that are currently not adequately and effectively treated.

No two patients are the same. Yet, currently, our algorithms make no allowance for individual differences. Treatments in psychiatry in general, and schizophrenia in particular, are chosen by ‘trial and error’ without reference to or guidance from the biological background of the individual. Yet, anyone who has treated patients knows that patients respond to one treatment, but not to another. Currently, we lack knowledge regarding reliable predictive (biological) markers nor do we have the associated technology to detect these markers for determining the most effective medication for an individual patient. Consequently, even if we would have at our disposal new treatments with alternative mechanisms, we lack the necessary knowledge and the associated diagnostic tools to individually tailor the treatment to the genetic profile of the patient. Thus, a critical challenge for the field (both to optimize current and to advance new treatments) is to develop the ability to deal with individual differences and the ability to predict who will respond to what and to develop biologically-informed, rather than DSM-IV-generic, treatments.

The likelihood of finding reliable biological markers is maximal if one chooses homogenous patients in a similar stage of disease. In this regard, the current study with its focus on a homogenous subset in a similar stage of disease (first episode patients early in their illness) and all provided with a uniform and specific treatment (amisulpride, a relatively clean D2/3 blocker, used in a standardized regimen) provides the ideal background against which one can detect biological markers predictive of outcome. Which particular markers to focus on, is a matter of legitimate debate. We have focussed on two broad strategies – a combination of technology driven (pharmacogenetics, proteomics and metabolomics markers) and hypothesis driven (neurochemical, glutamate imaging) markers.
In terms of empirical markers, we have chosen to evaluate pharmacogenetic, proteomic and metabolomic markers. These markers have been chosen as they provide a high-throughput and minimally invasive (only cheek-swab or blood-draw required) intervention and provide a comprehensive analysis. The main challenge with these markers is specificity. To overcome this we propose to apply advanced bioinformatics driven analysis, but, more empirically – a hypothesis generating set, the results from which will be confirmed in a hypothesis-testing set. In addition to empirical markers, we will also test imaging-derived hypothesis-driven markers. The choice of these markers is driven by the substantial progress in understanding the role of glutamate in schizophrenia, and the development of advanced techniques (MR Spectroscopy for glutamate) to measure them.
Aim: to test whether glutamatergic markers predict response to first and second line treatments, and if an empirical combination of pharmacogenetic, proteomics- and metabolomic markers can provide clinical valuable predictive value.

1.4 Testing the utility of MRI screening

A prerequisite for the optimal treatment of schizophrenia is the ability to predict treatment outcome and the exclusion of patients whose psychotic symptoms are not due to the disorder but to underlying 'organic' pathology, such as a cerebral tumour. Antipsychotic treatment in these patients is inappropriate and may delay the initiation of potentially life-saving medical intervention. Interestingly, despite its obvious importance, it is unknown whether a screening for organic pathology in first-episode schizophrenia makes medical and economic sense. Guidelines on this question (depending on the country issuing these) are either vague or non-existent. This study will address this issue by examining the clinical utility of MRI in a sample that is much larger than those previously studied, and that is representative of the population of patients presenting with first episode schizophrenia or schizophreniform psychosis across Europe. Exclusion of patients who do not have schizophrenia or other 'functional' psychoses (and will not respond to psychiatric treatment) through MRI at the point of first presentation will maximise the likelihood that antipsychotic treatment will be effective. To date, trials of treatment in schizophrenia have relied on clinical assessment to exclude organic psychoses: this will be the first study to employ neuroimaging for this purpose.
A second issue is whether MRI abnormalities at first presentation of schizophrenia can predict the response to subsequent treatment. Although a number of studies have reported that enlarged ventricles and reduced grey matter volume are associated with a relatively poor response, these studies have generally involved small samples in which treatment was administered naturalistically, with patients

receiving a range of different types and doses of antipsychotics. Moreover, many involved chronically ill patients that had previously been treated with antipsychotics.

To definitively assess the predictive value of MRI data requires a study in which previously untreated patients are scanned prior to the administration of a standard treatment, with their response assessed prospectively. Furthermore, the image analysis needs to use recently developed methods that take account of spatially distributed information in brain tissue data to achieve a better understanding of the differences between patients who do and do not respond to treatment.
Aim: to collect a systematic sample of 200, standardised, high-quality, MRI images from first episode patients with minimal prior exposure to medication to determine if an MRI in this population has medical and clinical utility.

1.5 Study objectives

The current trial has eight objectives that are summarized in table 1

Table 1. Objectives of OPTiMiSE.

	Objectives of the study
I	To test applicability of amisulpride as the first step in a treatment algorithm
II	To test guideline recommendation that non-responders to an antipsychotic drug benefit from a switch to an antipsychotic with a different receptor binding profile
III	To provide the acceptability and outcome data on the application of clozapine in non-responding patients within the first 10 weeks of their treatment initiation
IV	To test if an IT-enabled psycho-social intervention can improve treatment adherence and global functional outcome in first-episode schizophrenia patients
V	To test whether glutamatergic markers predict response to first and second line treatments
VI	To test if a combination of pharmacogenetic, proteomics- and metabolomic markers can provide clinical valuable predictive value
VII	To define the nature and prevalence of 'organic' pathology in patients presenting with a first episode schizophreniform psychosis
VIII	To determine the extent to which MRI measures at first presentation predict the therapeutic response to subsequent antipsychotic treatment

2. Rationale for the study

2.1 Rationale for design of the medication study

In this study, the first episode schizophrenia patients will initially all be treated with amisulpride. Our decision on which a particular drug should be prescribed to a first-episode patient in order to optimise symptom reduction and decrease the chance of treatment discontinuation, is partly based on the largest first episode schizophrenia study to date: EUFEST (Kahn et al. 2008).
The EUFEST-study included 498 subjects diagnosed with schizophrenia, schizophreniform, or schizoaffective disorder and randomly assigned the patients to haloperidol, amisulpride, olanzapine, quetiapine, or ziprasidone. Amisulpride and olanzapine did clearly best in terms of the primary outcome 'treatment discontinuation' due to any cause and the proportion of patients in remission applying the remission criteria defined by Andreasen et al.(2005). Furthermore, all second generation antipsychotic drugs including amisulpride and olanzapine were associated with fewer extrapyramidal side-effects than low-dose haloperidol.
Olanzapine and amisulpride are clearly effective first line agents with equivalent comparative efficacy according to five large randomised controlled trials including the Europe-wide randomised EUFEST study (Kahn et al. 2008, Lecrubier et al. 2006, Mortimer et al. 2004, Vanelle and Douki, 2006), a meta-analysis of studies comparing amisulpride and olanzapine head-to-head (Leucht et al. 2008a) and meta-analyses comparing both compounds with typical antipsychotics (Davis et al. 2003, Leucht et al. 2002). According to these reviews both compounds are among the most efficacious antipsychotic drugs. Both are atypical antipsychotic drugs with good overall tolerability and few extrapyramidal side-effects (Duggan et al. 2005, Leucht et al. 2002), but their receptor binding profiles are very different. In essence amisulpride is a selective dopamine antagonist with no significant effects on other receptors. Its atypical properties are mainly explained by mesolimbic selectivity. In contrast, olanzapine has action on various central receptors, but its atypical properties are mainly explained by a stronger antagonism of central serotonin than of central dopamine receptors (Bymaster et al. 1999, Perrault et al. 2000). This difference in receptor binding profiles is essential for our study.

In terms of atypical antipsychotics we had to choose two compounds with very different receptor binding profiles and similar efficacy. Amisulpride is an ideal choice here, because it is very different from all atypical antipsychotics being the only selective dopamine receptor antagonist (Perrault et al. 2000). Risperidone would have been another alternative, but its receptor-binding profile is less different from that of olanzapine (Bymaster et al. 1999). Olanzapine was chosen as another very efficacious atypical antipsychotic. There are some concerns supported by meta-analyses (Davis et al. 2003, Leucht et al. 2007c, Leucht et al. 2008a) that other atypical antipsychotic drugs such as aripiprazole, quetiapine or ziprasidone are somewhat less efficacious and any such difference in efficacy would jeopardize the aims of the study. Clozapine is even more efficacious than amisulpride or olanzapine, but its use is complex due to a risk of agranulocytosis, and many other side-effects such as hypotension, fevers, constipation, myocarditis making among others slow titration necessary.

If we had chosen a typical antipsychotic drug such as haloperidol the side-effect profile would have been too different making blinding a challenge. Despite the debate whether there really is a superiority of the atypical antipsychotic drugs it seems that

many patients do not accept typical antipsychotics such as haloperidol anymore making recruitment very difficult as was the case in a recent German multicenter study (Gaebel et al. 2007), this effect was also reported by Lieberman et al. 2005.

We decided to start patients on amisulpride, because olanzapine is associated with considerable weight gain and subsequent metabolic problems. Furthermore, amisulpride is available as a generic which is important from a cost-effectiveness perspective. Thus, we propose that amisulpride should be the first and rational step in a treatment algorithm.

However, we anticipate that 60% of the patients will not meet remission criteria by 4 weeks. Whether these patients can benefit from a switch to an antipsychotic featuring an alternative receptor binding profile is unclear. Our study will provide the first definitive answer to this question. The main aim is to finally address the (unproven) guideline recommendation that non-responders to an antipsychotic drug benefit from a switch to an antipsychotic with a different receptor binding profile. In light of this, non-responders to the initial four-week treatment with the selective dopamine antagonist amisulpride will either be continued on amisulpride (control group that 'stays') or switched to the multi-receptor antagonist olanzapine (intervention group) in a six-week double-blind trial. The duration of this double blind phase is in line with previous switch studies (e.g. Kinon et al., 2010), and comprises a reasonable time to prescribe an antipsychotic awaiting a response.

Thus, OPTiMiSE will examine the clinical utility of switching from a selective dopamine antagonist to a multireceptor antagonist (i.e. an antipsychotic with a different receptor binding profile) in the treatment of first-episode schizophrenia or schizophreniform disorder with the goal of reaching symptomatic remission in a maximum proportion of patients within 10 weeks of initiating treatment.

Even after phase II (10 weeks) we expect that about 25% of patients will not have reached remission. We will therefore offer these patients (open) treatment with clozapine. There is consensus and a lot of evidence that clozapine is the most efficacious antipsychotic drug, but it is associated with severe side-effects, especially potentially fatal agranulocytosis requiring weekly blood monitoring. Most treatment guidelines suggest that clozapine should be started after at least two other antipsychotic drugs that were given in sufficient doses and for a sufficient duration have failed. According to current recommendations, a patient who fails two trials of 6 weeks with an antipsychotic should be offered clozapine, which would imply that a first episode patient should be offered clozapine within 12 weeks of start of treatment. However, this is hardly ever the case: standard treatment evidence shows that the average patient being initiated on clozapine has often been psychotic for nearly 10-12 years! Recent data suggest however that clozapine can be systematically applied as the third line treatment within the first 6 months, and shows dramatic benefits for those who had failed two other atypical medications. Therefore we will explore whether treatment with clozapine will increase the number of first-episode patients who will reach remission after having failed adequate treatments with both amisulpride and olanzapine. Thus, OPTiMiSE will provide the acceptability and outcome data on the first systematic, large-scale, application of clozapine in non-responding patients within the first 12 weeks of their treatment initiation.

The choice of clozapine for the non-responders to both phases I and II is justified, because clozapine is generally considered to be the most efficacious compound in refractory patients by all treatment guidelines.

This has been documented by many single trials and meta-analyses (Kane et al. 1988; Leucht et al. 2009; McEvoy et al. 2006; Rosenheck et al. 1997; Wahlbeck et al. 1999). The evidence in first episode patients is more limited, but a recent small trial by the first episode team in Toronto showed that clozapine can be systematically applied within the first 6 months, and shows dramatic benefits for those who had failed other atypical medications (Agid et al. 2007).

2.2 Rationale for selection of the primary study endpoint “symptomatic remission”

Until some years ago, studies suffered from a lack of agreement on the best way to conceptualise response to treatment. Usually response was defined as a percentage reduction of a rating scale (PANSS, BPRS) total score, but many cut-offs have been used (20%, 30%, 40%, 50%) the lowest ones probably not being clinically significant. Furthermore, a PANSS reduction from 120 to 60 and from 60 to 30 both (after subtracting the 30 minimum PANSS points), are 50% reductions but the first patient is still much more ill than the second one. This issue was tackled by the Schizophrenia Working Group who developed a consensus definition of remission. Symptomatic remission will be defined according to the criteria of Andreasen et al. (2005): 8 specific symptoms (PANSS items P1, P2, P3, N1, N4, N6, G5 and G9) of schizophrenia as measured by the Positive and Negative Syndrome Scale (Kay et al. 1987) are at the most only mildly present (maximum rating of “3”) so that they do not interfere with daily life functioning. This definition of remission shows good clinical validity and is associated with clinical and quality of life outcomes (see below). It has also been shown to be a realistic goal of antipsychotic drug treatment. Importantly, in the European First Episode Schizophrenia Trial (EUFEST) study, 40% of first-episode patients treated with amisulpride and olanzapine reached the new remission criteria within the first four weeks, supported by other findings.

Since the introduction by Andreasen et a in 2005 numerous studies have shown that the remission criteria are strongly associated with clinically valid outcomes such as quality of life, social and occupational functioning, cognitive functioning, subjective well-being and maintenance of symptomatic stability (De Hert et al. 2007, Ciudad et al.2009, Dunayevich et al. 2006, Helldin et al. 2006, Helldin et al. 2007, Lambert et al.2006, San et al. 2007, Emsley et al. 2007, Nasrallah and Lasser 2006, Opler et al. 2007, van Os et al. 2006). Analyses of large databases showed that they are an achievable and realistic goal in antipsychotic drug trials (Leucht et al. 2007a). We will not analyse the time criterion of the remission criteria which only applies to long-term studies. Another advantage of these remission criteria is that they are easier to interpret than the mean change from baseline to endpoint of the PANSS. A symptomatic remission is also a harder outcome than a mean change of a rating scale. As remission means that key symptoms of schizophrenia are at the most only mildly present, such patients usually do not need further hospitalization. Therefore, this outcome will also emphasize the cost aspect of the early switching strategy.

In summary, the new remission criteria are a clinically meaningful primary outcome and their use will facilitate translating the study results into practice guidelines.

2.3 Rationale for selection of Study Population

Although antipsychotics have been used in the treatment of schizophrenia for over half a century it is still not known whether switching from one antipsychotic to another is useful in patients who fail treatment with the first drug. In fact, studies that examined this issue are few and far between and are hampered by small sample sizes and methodological limitations. This paucity of studies is even more pronounced for people with a first episode of schizophrenia, although the first episode is a crucial stage of the illness where rapid and effective treatment is considered key for the subsequent clinical course and long-term outcome. Despite the lack of sound prospective studies on this question, treatment guidelines usually recommend switching to an antipsychotic drug with a different receptor binding profile in case the initial antipsychotic failed, but the underlying assumption has never been proven in an adequate trial. This is one of the objectives of the current trial.

2.4 Rationale for studying biological predictors

One of the major shortcomings in the current treatment of schizophrenia is that we have no valid criteria in clinical practice to decide which form of treatment should be chosen first. The identification of blood based biological markers of drug response with a good sensitivity and specificity would enable the physician to use these tests prior to choosing the antipsychotic treatment and therefore help the practitioner in his daily clinical practice. Secondly, the identification of these markers will help to identify new and more specific pharmacological targets as it will indicate which pathways are implicated in drug response. Currently, studies of biomarkers have been mostly performed in the field of candidate genes, and it has to be acknowledged that the overall yield has been disappointing. The few robust results have been in relation to side-effects, e.g., association of the DRD3 variant with extra-pyramidal symptoms, but no single biomarker can be considered to be strongly associated with drug efficacy. This lack of success is not surprising as most studies focused on only a few candidate genes, mainly dopaminergic receptors and transporters and serotoninergic receptors, not taking in consideration the large number of potential pharmacodynamic and pharmacokinetic targets which may be implicated in antipsychotic action either in terms of efficacy or tolerance. The second main weakness of these studies has been the quality of the clinical assessment. Drug response has been mostly measured retrospectively in very inhomogeneous cohorts mixing together first psychotic episodes and chronic schizophrenia patients. Finally, studies to date have examined the usual candidate genes, but have ignored the vast amount of literature and determinants known to influence pharmacokinetic and pharmacodynamic aspects. To overcome this we will use a special pharmaco-genetic (PG) chip developed at INSERM. This PG-chip, which is dedicated to genotyping 15,000 polymorphisms, makes it possible to reconstruct the haplotype diversity of 1292 genes implicated in the metabolism, transportation, and targeting of drugs as well as to genotype the functional polymorphisms that are indispensable for certain genes which are not included in GWA chips. This is a tool at the intermediate scale between a low-throughput candidate gene approach, and a pan-genomic approach, for which virtually no pharmacogenetic cohort has sufficient power. This PG chip includes genes implicated in drug metabolism, drug transport, inflammation (including 158 HLA genes), metabolism, apoptosis, inflammation, chemokines, cytokines, brain receptors and other proteins, signal transduction (carcinogenesis), and DNA repair. The OPTIMISE trial will make it possible to overcome the limitations of the previous

studies. A) We will begin with a set of homogenous patients – by focussing on first episode patients at similar stage of disease. ; B) we will provide a uniform standardised treatment on the first step; C) we will provide relatively straight forward receptor blockage by choosing amisulpride, a relatively specific D2 blocker, and D) we will have a broad series of pharmacokinetic and pharmacodynamic markers so that we provide coverage for more potential predictors than the traditional dopamine/serotonin based markers in previous studies.

Pharmacogenetics measures a fixed trait variable, whereas response in patients is likely determined by a mixture of fixed traits and dynamic variables. It is in this regard that focusing on distal and dynamic variables is equally relevant. There are several options to measure this dynamic profile. We will look at the pattern of protein and metabolic expression changes that are induced by the drug and use those to infer mechanisms and predict response. It should be acknowledged, that at this stage all these methods remain exploratory. However, we have chosen to focus on 'proteomic', 'metabolomic' and 'inflammatory' approaches as these are the level of biology that is most proximal (as compared to genotype and gene-expression) to phenotypic outcome.

Proteomics in relation to treatment response (pharmacoproteomics) is an emerging field. Holmes et al. (2006) found that metabolic profiles showed a highly significant separation of patients with first-onset schizophrenia from healthy controls. That short-term treatment with antipsychotic medication resulted in a normalization of the disease signature in over half the patients indicates the potential for biomarkers as monitors for clinical treatment. However, the Holmes et al. (2006) sample was small, the treatment not fully controlled and the drugs used had multiple modes of action. We have two unique opportunities in our study. First, for the reasons mentioned above we will have data on a homogenous population, with standardized treatment and a specific agent – something that has been lacking in previous studies. Second, we will have sufficient size to undertake a 'hypothesis-generating' sample, followed by a 'hypothesis-testing' sample – thus providing us with sufficient rigour to make some conclusion. The discovery phase of the project will focus on the identification of novel specific biomarker patterns relevant to predicting and/or monitoring patient response to amisulpride treatment in serum/plasma, using 30 responders and 30 non-responders matched for ethnicity, gender and age. In the discovery phase two-dimensional gel electrophoresis will be used followed by labeled MS based discovery, which is more sensitive than label free methods. Any findings will be validated in an additional set of responders and non-responders by direct MS multiple reaction monitoring and immunodetection methods.

Metabolomics can also provide valuable information about disease pathogenesis and result in metabolic signatures that could be developed as biomarkers for disease and progression. Pharmacometabolomics is emerging as a new field that could complement pharmacogenomics by providing precise intermediate phenotypes for drug response. Metabolomics could add significantly to our understanding of both pharmacokinetic and pharmacodynamic properties of drugs. We will use a method of targeted analysis of metabolites with high throughput quantitative mass spectrometry. This is a new and versatile tool for comprehensive analysis of large populations which includes lipids, sugars, and amino acids and many other analytes.

There is considerable evidence that schizophrenia is associated with immune system dysregulation. For example, blood and cerebrospinal fluid (CSF) levels of proinflammatory cytokines are significantly increased in schizophrenic patients, and their normalization correlates with improvement in psychotic symptoms. Among schizophrenic patients, significant correlations between the levels of antigens issued

from HERV.W virus (GAG or ENV proteins) present in the blood and the levels of C-reactive protein (CRP), which is considered as a hallmark marker for systemic inflammation, were identified. Some evidence also indicates that typical and atypical antipsychotics modulate immune function in vitro and in vivo studies and have anti-inflammatory properties. We will therefore also study some inflammatory parameters during the OPTIMISE trial. The status of systemic inflammation will be determined by standard ELISA for C-Reactive Protein (CRP). The activation of the blood complement will be followed by the dosage of complement components (C1, C3, C4) by the mean of ELISA or functional standards assays. Several cytokines will be measured by standard ELISA in the blood, including those indicative of the immune and inflammatory status, such as the pro-inflammatory cytokines (IL1, IL6, IL8, TNF-alfa, TGF-alfa and those indicative of the lymphocyte response commitment such as Th1 type cytokines (IFN-alfa), Th2 type (IL4, IL10) and Th17 type (IL17).
The final biological predictor we will assess will be regional brain glutamate levels, as measured using MR Spectroscopy. A proportion of patients with schizophrenia do not respond well to treatment with antipsychotic drugs. This could be because, in these patients, dysfunction of the brain glutamate system is particularly important to their illness. As a result, treatment with antipsychotic drugs, which usually act on brain dopamine recptors but have little impact on the glutamate system, may be relatively ineffective. We aim to use MR spectroscopy to measure brain glutamate in a subgroup of the total sample. We predict that patients with a prominent disturbance of glutamate levels will be particularly unlikey to respond to treatment with amisulipiride, which only acts on the dopamine system.

2.5 Rationale for the Psychosocial intervention

The response rate to antipsychotic medication in first episode patients is high (Kahn et al, 2008). Maintenance treatment is effective in maintaining remission and reducing relapse rates by five fold after this (Robinson et al, 2003). Strategies such as intermittent, targeted treatment after the first episode appear not be as effective as continuous maintenance treatment (Wunderink et al, 2007) in preventing relapse. However, the real-life effectiveness of maintenance treatment is limited by high rates of non-adherence after the first episode, at 50% or higher during the first year. Negative attitudes to medication, perceived lack of efficacy, substance use, lack of insight, cognitive impairments and side effects (Mutsatsa et al 2003; le Quach et al 2008) have been shown to contribute to non-adherence.

Definitions of poor adherence vary but 42-60% of first episode sufferers show poor adherence in naturalistic cohorts followed-up for one year or more (Verdoux et al, 2002, Mojtabai et al, 2002, Coldham et al, 2002). Poor adherence with treatment is a particular challenge in the first year compared to later stages of illness because placebo controlled trials show a greater benefit of antipsychotics in first episode treatment and first relapse prevention. Attention and time paid to therapeutic alliance at this stage may be returned later on. Several important elements in non adherence can be identified: lack of insight, negative attitude to medication, no perceived benefits, lack of family support and side effects (Kampman et al, 2002, Mutsatsa et al, 2003, Perkins et al, 2006). We will evaluate the effectiveness in maintaining remission of an IT-enabled programme comprising three elements: web-based psycho-education; a motivational intervention package; and electronic medication alerts and updates. The effectiveness of this programme will also be investigated within a group of non-remitted patients; as the elements of non-adherence may be

especially present in these patients, we cannot justify excluding non-remitted patients from this study. If they wish, they may be randomized into the psychosocial intervention component.

2.6 Rationale for the MRI measurements

The proportion of patients presenting with a first episode psychosis due to underlying organic pathology has been estimated in different studies at 1-10% (Woolley & McGuire, 2005; McGuire, 2007). The most effective means of detecting organic causes of psychosis is MRI scanning, and inclusion of MRI in the initial assessment of psychosis is considered good practice in most economically developed countries (American Psychiatric Association, 2004; Royal Australian & New Zealand Psychiatric Association, 2005). In the UK, NICE recently considered whether an MRI scan should be a routine part of the assessment of all new patients with psychosis, but deferred making a decision as the existing literature comprises studies of small, potentially unrepresentative samples (http://www.nice.org.uk/TA136). There is thus a need for a study that will determine the true prevalence of organic causes of first episode psychosis and shape future clinical management in this area.

OPTiMiSE will address this issue by examining the clinical utility of MRI in a sample that is much larger than those previously studied, and that is representative of the population of patients presenting with first episode schizophreniform psychosis across Europe. Exclusion of patients who do not have schizophrenia or other 'functional' psychoses (and will not respond to psychiatric treatment) through MRI at the point of first presentation will maximise the likelihood that antipsychotic treatment will be effective. To date, trials of treatment in schizophrenia have relied on clinical assessment to exclude organic psychoses: this will be the first study to employ neuroimaging for this purpose.

A second aim within the scope of this objective is to evaluate whether the severity of volumetric MRI abnormalities (as identified using voxel-based morphometry (VBM)) or a particular topographic distribution of alterations in regional grey matter volume (as identified with a pattern recognition approach) at first presentation of schizophrenia can predict the response to subsequent treatment. A number of studies have reported that ventriculomegaly (Weinberger et al, 1980; Schulz et al, 1983), and reduced total (Zipursky et al, 1998) and reduced regional (Molina et al, 2003) grey matter volume are associated with a relatively poor response. However, these studies have generally involved small samples (n=12-45) in which treatment was administered naturalistically, with patients receiving a range of different types and doses of antipsychotics (Friedman et al, 1992). Moreover, many involved chronically ill patients who had previously been treated with other antipsychotics. To date, neuroimaging studies have related therapeutic response to differences that are localised in space and linear in nature, such as the volume of a particular brain region. However, the neuroanatomical changes that are associated with schizophrenia are subtle and spatially distributed, and may be more readily detected using image analysis methods that employ spatially distributed information (Davatzikos 2004), such as a Support Vector Machine (SVM) approach. To definitively assess the predictive value of MRI data requires a study in which previously untreated patients are scanned prior to the administration of a standard treatment, with their response assessed prospectively in a double-blind fashion.

Furthermore, the image analysis needs to use recently developed methods that take account of spatially distributed information in brain tissue data to achieve a better understanding of the differences between patients who do and do not respond to treatment.

By applying these methods to MRI data at first presentation, and relating this to the subsequent response to a single antipsychotic drug, OPTiMiSe will provide for first-of-its kind, methodologically sound evidence of MRI as a clinical predictor of antipsychotic response.

OPTiMiSe will thus use state of the art MRI technology to study a representative sample of patients with first episode of schizophrenia who have not previously had a course of antipsychotic treatment, and from which patients with 'organic' psychoses have already been excluded. Patients will be scanned prior to treatment with amisulpride, administered according to a standardised dosing regimen. The proposed sample of n=200 represents the largest ever sample of patients with schizophrenia to be studied with MRI, and will provide sufficient power to determine the true prevalence of 'organic' psychoses in this population, and the extent to which the severity of volumetric abnormalities predicts the subsequent clinical response.

It is expected that the study will provide: 1) A definitive assessment of the proportion of patients presenting with first episode psychosis that have an 'organic' aetiology (that requires non-psychiatric treatment); 2) A definitive assessment of the ability of MRI to predict response to treatment in schizophrenia. These are likely to be a key reference points for national guidelines for the optimal treatment of schizophrenia.

3. Study design

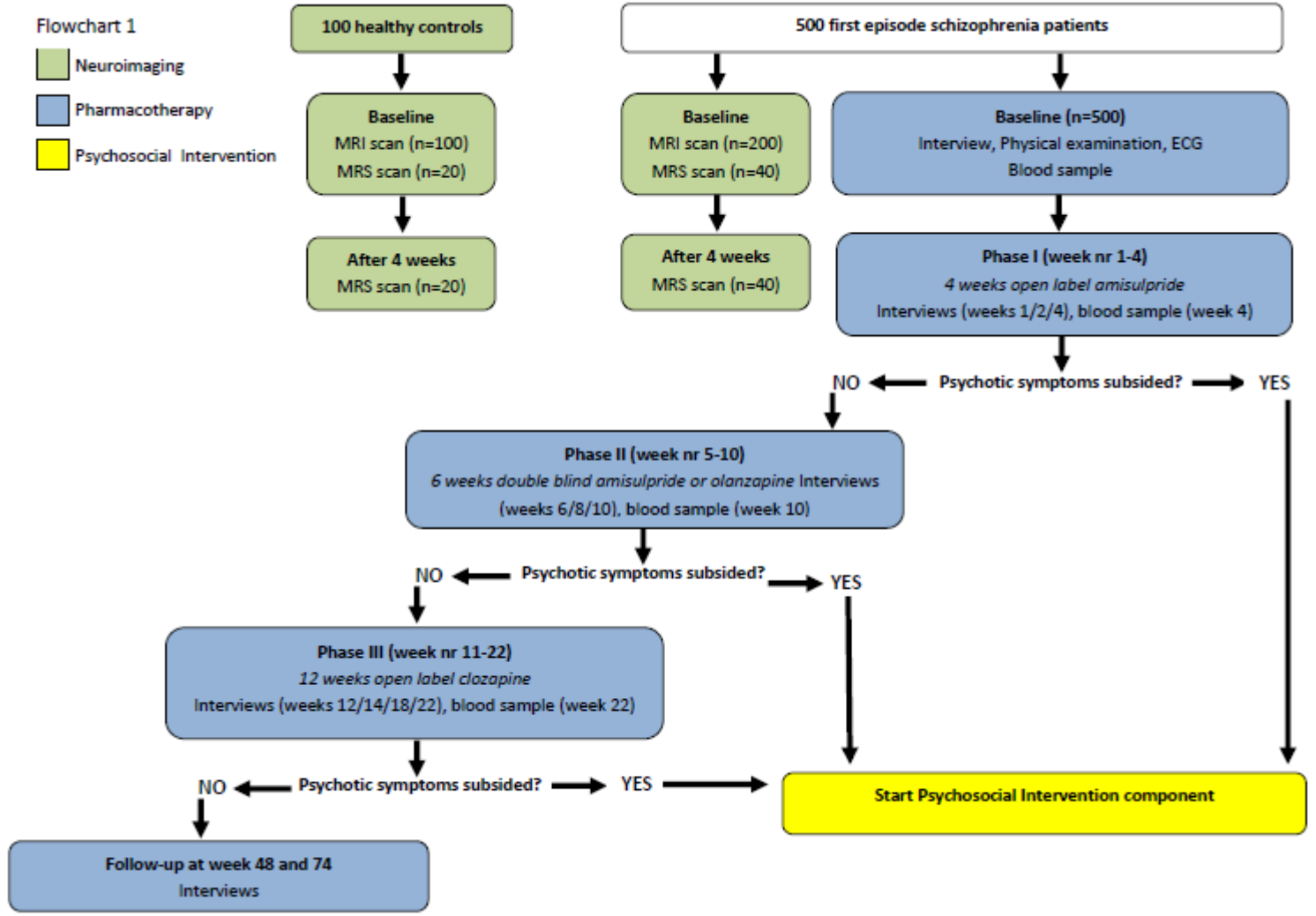
In the current study 500 patients with a first episode of schizophrenia or the diagnosis schizophreniform / schizoaffective disorder will be included From 200 of these 500 patients, MRI will be acquired at screening to check for neurological disorders. In addition, spectroscopy will be performed at selected centres in 40 patients. This spectroscopy will be repeated 4 weeks after treatment.

All 500 patients will enter a four week open-label treatment with the anti-psychotic amisulpride (phase I). Those patients who are not in symptomatic remission at the end of these four weeks enter a 6-week, randomised, double-blind phase of either continuation of amisulpride or switching to olanzapine (phase II). Those patients who are still not in symptomatic remission at the end of this phase are treated with open-label clozapine for 12-weeks (phase III).

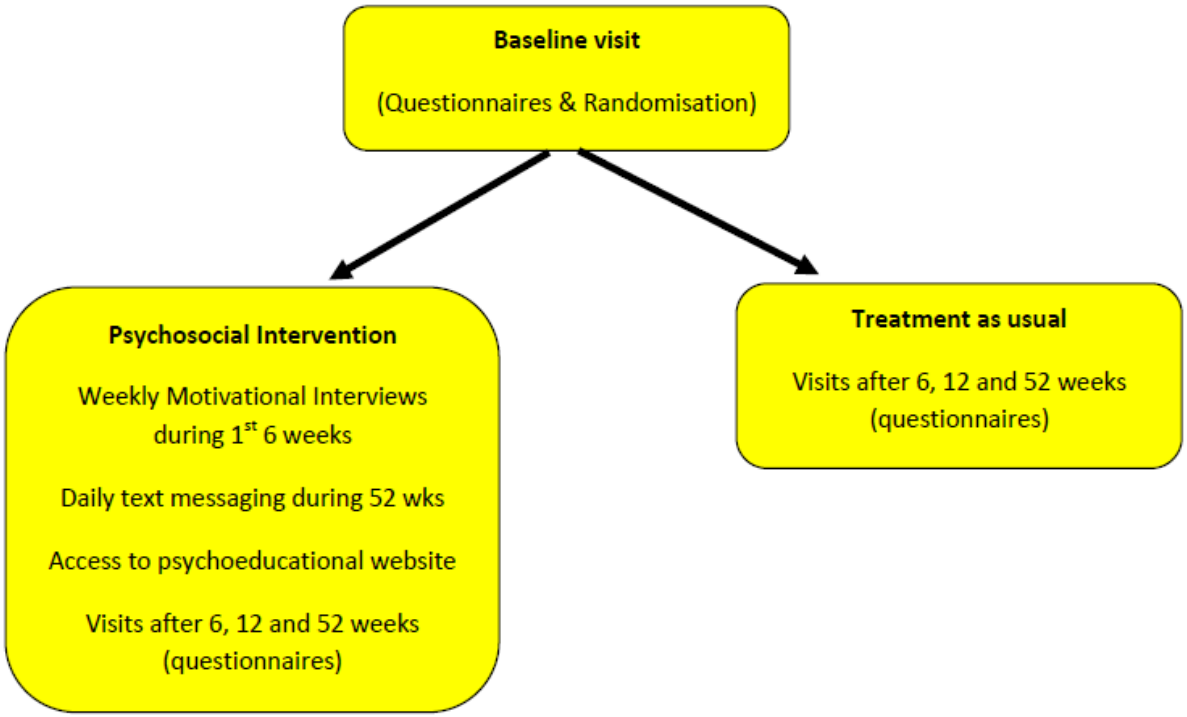
Assignment to a treatment option in phase II of the study will be performed randomly to eliminate the possible influence of arbitrary delegation of patients on the study results. This is also done to evenly distribute known and currently unknown factors potentially influencing outcomes (such as demographic factors or findings at the baseline examination), which increases the validity of statistical analyses. The double-blind administration of medication is done to minimise the influence of expectancy regarding the type of medication on the measurement of clinical parameters and data collection. Antipsychotic treatment in phase I and phase III of the study is open-label as no alternative treatment option is available in these phases (uncontrolled study setting).

The study flow and assessments that will be performed are depicted schematically in Flowchart 1.

Patients in symptomatic remission, as defined by the criteria of Andreasen et al. (2005) at each stage of the trial, including those responding to the initial 4 week open-label treatment with amisulpride, those on amisulpride or olanzapine after the additional 6-week double-blind treatment phase, and those responding to 12-weeks open label clozapine treatment will be randomized to receive either a 12-week psychosocial treatment intended to increase medication adherence or to treatment as usual. The psychosocial adherence programme includes 3 components: psycho-education of participant and (where available) family using web-based materials, motivational interviewing sessions and medication alerts and simple messaging and web interface via mobile phone. The effectiveness of this programme will also be investigated within a group of patients that are not remitted. These patients are either at the end of the pharmacological component or have dropped out during one of the phases of this component. If they wish, they may be randomized into the psychosocial intervention component. The study flow and assessments that will be performed for the psychosocial intervention are depicted schematically in Flowchart 2.


Flowchart 1
Neuroimaging
Pharmacotherapy
Psychosocial Intervention
100 healthy controls
Baseline
MRI scan (n=100)
MRS scan (n=20)
After 4 weeks
MRS scan (n=20)
500 first episode schizophrenia patients
Baseline
MRI scan (n=200)
MRS scan (n=40)
After 4 weeks
MRS scan (n=40)
Baseline (n=500)
Interview, Physical examination, ECG
Blood sample
Phase I (week nr 1-4)
4 weeks open label amisulpride
Interviews (weeks 1/2/4), blood sample (week 4)
NO
Psychotic symptoms subsided?
YES
Phase II (week nr 5-10)
6 weeks double blind amisulpride or olanzapine Interviews
(weeks 6/8/10), blood sample (week 10)
NO
Psychotic symptoms subsided?
YES
Phase III (week nr 11-22)
12 weeks open label clozapine
Interviews (weeks 12/14/18/22), blood sample (week 22)
NO
Psychotic symptoms subsided?
YES
Start Psychosocial Intervention component
Follow-up at week 48 and 74
Interviews

Flowchart 2: Psychosocial Intervention



4. Study population

4.1 Population

This study will include 500 patients with a first episode of schizophrenia or the diagnosis schizophreniform disorder. All patients fulfilling the inclusion and exclusion criteria as described below may, after a detailed description by a doctor and the written declaration of informed consent, participate in the study.
200 of these 500 patients, in selected centers, will participate in the MRI part of the study.
The MRI part of the study will also include 100 healthy controls, matched to the patient sample for age, gender, ethnicity, IQ and parental social class. Controls will be recruited by advertisements from each site in a similar proportion to the patients. These subjects will undergo the same MRI measurement as the patients, but will not participate in other parts of the study.

4.2 Inclusion Criteria

- Diagnosis of schizophrenia, schizophreniform or schizoaffective disorder as defined by DSM-IV on the basis of the Mini International Neuropsychiatric Interview Plus (M.I.N.I. Plus; Sheehan et al. 1998). Schizophreniform disorder is assessed through a M.I.N.I. diagnosis of psychosis NOS complemented by a diagnosis of schizophreniform disorder according to DSM-IV criteria.
- Age 18-40 years
- Written informed consent.
- Female patients of childbearing potential need to utilize a proper method of contraception (the pill, vaginal ring, hormonal patch, intrauterine device, cervical cape, condom, contraceptive injection, diaphragm, abstinence).

4.3 Exclusion criteria

- A time interval between the onset of psychosis and study entry exceeding two years.
- Prior use of antipsychotic medication longer than an episode of two weeks in the previous year and/or 6 weeks lifetime.
- Intolerance to one of the drugs in this study.
- Patients who are coercively treated at a psychiatric ward (based on a judicial ruling)
- Patients who are represented by a legal guardian or under legal custody
- The presence of one or more of the contraindications against any of the study drugs as mentioned in the IB texts (listed in Appendix B).
- Pregnancy, as determined through a pregnancy test, or lactation

Additional exclusion criterion, specifically for patients and healthy controls participating in MRI/MRS procedures (if patients meet this exclusion criterion, they can still participate in the remainder of the study):

- Presence of any contraindication to MRI scanning (e.g. implanted metallic object or electronic device)

4.4 Sample size and power calculation

Power calculation for objective I, II and III: Finding evidence for pharmacotherapy guidelines in first episode schizophrenia

The first phase of this study will include 500 first-episode patients. Data of the EUFEST study, which is one of the largest first-episode trials to date, showed that about 40% of the patients on amisulpride were in symptomatic remission (as defined by Andreasen et al. 2005) within four weeks which therefore seemed a realistic goal for phase I in which all patients will be treated for four weeks with amisulpride. This assumption would require 350 patients to be enrolled into the study. However, halfway through the study almost 60% of phase I patients met remission criteria. Subsequently, the power analyses was adjusted to the following:

Statistical power phase II

After these four weeks, we will classify patients who are in symptomatic remission within four weeks (~60%) as responders. The patients who are not in symptomatic remission within four weeks (~40%) will be classified as non-responders. We will test whether symptomatic remission rate is improved in patients who are switched to olanzapine in comparison to patients who stay on amisulpride (phase II). Based on EUFEST we expect that 50% of the four-week non-responders who stay on amisulpride will be in symptomatic remission after another six weeks of treatment (10 weeks from treatment initiation). If the percentage of patients in remission increases from 50% to 70% as a result of switching to olanzapine (which is an estimation, as there are no prior studies on this topic), the two treatment arms will have to contain 90 patients each to obtain a statistical power of .79 with a type-I error rate of .05. If we consider that the drop out rate is approximately 30% and the remission rate is 60% (both observations after 250 patients have been enrolled into the study), than this implies that at least 487 patients will have to be included at baseline, taking into account a drop-out of 30% during phase II (observation in first 50 phase II patients).

Power calculation for objective IV: Finding psycho-social interventions to improve medication adherence

A power calculation based on non-adherence shows that, with a 2 tailed alpha of 0.05, a sample size of 180 (264 randomised with a 30% dropout rate), would have 90% power to show a reduction in non-adherence rates from 50% with routine care to 25% in the psychosocial program arm. If dropout rates are 20%, power increases to 96%. With the functional outcome, n=180 would have over 80% power to detect a 10 point difference in mean GAF score (common GAF SD 19, data from SoCRATES trial). When the remission rates and drop out rates during the study indicate that 180 patients can be expected to complete the psychosocial intervention component, inclusion of new subjects into this component will be closed.

Power calculation for objective V and VI: Finding biological predictors of treatment response

Our decision on the number of participating centres was based on the sample size required to test our hypothesis and the expertise and infrastructure available at each site. We have based our sample size on our primary predictive variable of $r > 0.6$, with a Type I error of < 0.05 and a power of 80% (Type II error of < 0.2). Under these conditions we will need 32 completed subjects with baseline scans and final ratings, and assuming a 20% dropout rate, we seek 40 subjects for 32 completers.

Given that this is an intensive study, and assuming that 33% of participants who take part in the clinical protocol at a given Centre will also agree to take part in this

neuroimaging study – we have selected Centres which have a combination of well established first episode programs and a track record of successful MRS imaging studies in schizophrenia. We expect that of the 32 subjects who will complete the baseline imaging and clinical part of the trial, 20-25 would be willing to undergo a second scan to examine the effect of treatment and this would provide us with an ability to detect correlations of r>0.7 between change in glutamate parameters and treatment outcome with a Type I error of < 0.05 and a power of 80% (Type II error of < 0.2).

We have since analysed the MRS data collected until March 2013 and recalculated the power analyses using the values from these data. The data until March 2013 showed a true difference in mean glutamate levels (scaled to creatine) between responders and non-responders as 0.25, associated with a standard deviation of 0.31. Power analysis was performed using these values and following parameters: 2 tailed t-test, alpha = 0.05, power = 0.8, ratio of responders: non-responders = 6:4. This returns a total sample size of 52 completed subjects, estimated to comprise of 31 responders and 21 non-responders. Using the same 20% drop-out rate we therefore seek 63 subjects for 52 completers. The increase from our additional estimate is likely due to additional variability arising from data acquisition using multiple MRI scanners. While we are still collecting empirical data on this variability, the revised power analysis inherently accounts for this, as it is based on actual multi-centre data.

65% of subjects recruited to March 2013 also completed a second MRS scan. This suggests a total of 34 subjects would be willing to undergo a second scan from a sample of 52. Using the same drop-out rate, we estimate 22 of these subjects would be willing to undergo a third MRS scan. Based on the same data as above, to detect a within-subjects change in glutamate levels of 0.2, power analysis suggests that follow-up scans in 20 subjects (alpha = 0.05; power = 0.8; SD =0.31) are required.

For the biological markers the power calculation was based on genetic predictors as they are the most studied at the time. The sample size (500 patients) will provide us with an ability of detecting an Odds Ratio of 1.9 with a Type I error of < 0.05 and a power of 86% (Type II error of < 0.14) when comparing responders and non-responders at Week 4. For that we hypothesize that the proportion of responders will be around 60%.

Power calculation for objective VII and VIII: Testing the utility of MRI screening
The effect size for volumetric data predicting treatment response in schizophrenia varies widely between studies, which may have been due to differences in the samples investigated in these studies, with the largest effect size (3.1) in a study of younger patients with a relatively brief history of previous treatment. The effect size for differences in cortical grey matter volume between good and poor responders in a first episode schizophrenia sample was approximately 0.75. In the volumetric analysis, assuming a more modest effect size or 0.5, at a statistical threshold of p=0.05, we would require subgroups of n=63 subjects to detect differences between responders and non-responders at 80% power. The minimum number of subjects needed for training and testing classifiers in order to obtain a statistically significant sensitivity and specificity in pattern recognition approaches has yet to be investigated. However, a number of studies have demonstrated that it is possible to obtain a good classification of subjects with sample sizes of 30 - 70. Thus, in the

current sample of 200 patients, we will have substantial statistical power to detect differences between responders and non-responders.

5. Primary and secondary study endpoints

For all four main goals of the study (described in section 1), the primary and secondary endpoints are defined below:

5.1 Primary study endpoint

I Finding evidence for pharmacotherapy guidelines in first episode schizophrenia

The primary outcome is the number of participants in remission at the end of phase I (4 weeks open treatment with amisulpride), phase II (double-blind treatment with amisulpride or olanzapine, comparison between arms) and phase III (open treatment with clozapine). Symptomatic remission will be defined according to the criteria of Andreasen et al. (2005): 8 specific symptoms (PANSS items P1, P2, P3, N1, N4, N6, G5 and G9) of schizophrenia as measured by the Positive and Negative Syndrome Scale (Kay et al. 1987) are at the most only mildly present (maximum rating of "3") so that they do not interfere with daily life functioning. The PANSS itself is a validated measure (Kay et al. 1987) and it is the most widely used scale to assess the symptoms of schizophrenia.

II Finding interventions to improve medication adherence

The primary outcomes will be (i) drug adherence rates defined categorically (adherent vs non-adherent) as a function of standardised self report and Sellwood rating scales; and (ii) global functioning (SOFAS score) at 1 year. Based on self report, the most widespread definitions of non-adherence are (a) stopping medication for at least one week during follow up (b) taking the prescribed drug less than 90% of the time.

III Finding biological predictors of treatment response

The primary outcome for biological predictors will be drug response defined categorically (remission vs non-remission) as a function of biological profile (eg: presence or absence of genetic variants, proteomic profile, metabolomic profile, immunologic profile). The primary outcomes of the MRS scans are the difference between responders and non-responders in regional glutamate levels a) at baseline and b) between baseline and after one month of treatment with amisulpiride.
We will addionally acquire a third MRS scan after 10 weeks of treatment (end of Phase II) to determine whether a) in patients randomised to amisulpride in phase II whether changes in glutamate take some time longer to appear, by comparing baseline and 10 week data and b) comparing second (end of phase 1) and third scans (end of phase 2) in patients randomised to amisulpride versus olanzapine in phase II whether a multireceptor agent (olanzapine) has greater effect on glutamate than a dopaminergic agent (amisulpride).

IV Testing the utility of MRI screening

Primary outcome is the percentage of first episode patients that show radiological abnormalities suggestive of neurological disorders which may explain the occurrence of psychotic symptoms.

5.2 Secondary study endpoints

I Finding evidence for pharmacotherapy guidelines in first episode schizophrenia

The secondary outcome measure is all-cause treatment discontinuation. Number and reason for premature discontinuations (treatment discontinuation) of the amisulpride and the olanzapine group will be compared.
Other measures which are included are the severity and improvement subscores of the Clinical Global Impressions Scale (CGI; Guy 1976) which will assess the overall severity and improvement of the participants. Levels of depression will be assessed with the Calgary Depression Scale for Schizophrenia (CDSS, Addington). The Global Assessment of Functioning scale (GAF; Jones et al. 1995) will be used to assess social functioning. The UKU side effects rating scale will be used to assess adverse effects of antipsychotic medication (Lingjaerde et al., 1987). We will assess weight gain, abdominal circumference and further adverse events with open interviews. The safety and tolerability of the study drugs will be monitored by the frequency and severity of side-effects.

II Finding interventions to improve medication adherence

Two process measures will also be used at baseline and 3 months, to test whether any improvements in adherence seen in the psychosocial intervention group can be attributed to the interventions: psycho-education assessed by Knowledge About Psychosis Scale (adapted from KASI scale and MI assessed by Drug Attitude Inventory (DAI-30). Secondary analyses include a comparison of all-cause treatment discontinuation between treatment groups as well as further investigation of adherence improvements in the group of patients that entered this component while not being in remission versus those who were in remission.

III **Finding biological predictors of treatment response**

The secondary outcomes are:
1. the ability of biological markers to predict response to antipsychotic in schizophrenia considered as a continuous variable (percentage of diminution of the PANSS total and sub-scores)
2. the ability of biological markers to predict antipsychotic treatment tolerability.

IV Testing the utility of MRI screening

The secondary outcome is the ability of MRI to predict response to antipsychotic treatment in schizophrenia.

6. Treatment of subjects

6.1 Treatment strategy and dosing

Dosing of study drugs

The dose ranges of the study medication in acutely ill patients with schizophrenia are well documented. Amisulpride will be given in doses between 200 and 800 mg/day (target dose 400 mg/day), for olanzapine the dose range will be 5-20mg/day. The

dose range of clozapine will be 100-900mg/day (Kane et al. 1988). The distribution of the doses over the day will be at the discretion of the investigators.

Phase I

After screening and inclusion in the study, the participants will receive open-label treatment with amisulpride in the first week. The following titration schedule is suggested, but variations are allowed as long as the patient is at a dose of amisulpride of 200, 400, 600 or 800 mg at the end of phase I. Intermediate dosage (i.e., 100, 300, 500 or 700) will cause serious problems in the transition to double blind phase II medication. Suggested titration:

- start with 100mg (half a tablet)
- day 4: increase to 200mg
- day 8: increase to 300mg
- day 12: increase to 400mg

For some patients, the target dose of 400mg may not be tolerated. In these patients, a stable dose of 200mg can be used. However, a dose decrease should only be chosen if a patient suffers side-effects. In others, 400mg may not be sufficient, in which case the dose of 600 or 800mg may be preferred.

Phase II

Those patients who are in symptomatic remission at the end of Phase I according to the criteria by Andreasen et al. (2005) will be randomized to either the psycho-social intervention to increase adherence or to treatment as usual (see section 9.2.2).

Those patients who are not in symptomatic remission will be randomized to six weeks double-blind treatment with either amisulpride at flexible doses between 200 and 800 mg/day, or olanzapine with flexible doses between 5 and 20mg/day. In the control group of patients staying on amisulpride, the patients will receive the same amount and size of capsules as in the olanzapine group to maintain the blind. This is accomplished by the creation of capsules which contain either 5mg of olanzapine or 200 mg of amisulpride. At the start of phase II, patients will receive one capsule per day instead of one 200mg tablet of amisulpride of their previous dosing in phase I. Switching from phase I to phase II will occur between day 1 and day 7 of phase II, dependent on the dose a patient receives in phase I. Titration of the tablets amisulpride to the capsules amisulpride or olanzapine is described in Table 2 below. The left column provides the 4 possible amisulpride dosages at the end of phase I (200, 400, 600 and 800 mg/day); on the respective rows the titration schedule for the first 7 days of phase II are provided. For instance, if a non-responder used 400 mg/day at the end of phase I, this patient will continue to use 2 tablets a day for the first 2 days of phase II, replace one tablet with one capsule per day on days 3 and 4, and stop using the tablets altogether on day 5, only using capsules in a dosage that is equal to the dosage used at the end of phase I.

Table 2. Titration schedule from tablets (phase I) to capsules (phase II)

Amisulpride daily dose in phase I	Day of phase II						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
200mg/ day	1 tablet 0 capsules	1 tablet 0 capsules	1 tablet 0 capsules	0 tablet 1 capsule	0 tablet 1 capsule	0 tablet 1 capsule	0 tablets 1 capsule
400mg/ day	2 tablets 0 capsules	2 tablets 0 capsules	1 tablet 1 capsule	1 tablet 1 capsule	0 tablets 2 capsules	0 tablets 2 capsules	0 tablets 2 capsules
600mg/ day	3 tablets 0 capsules	2 tablets 1 capsule	2 tablets 1 capsule	1 tablet 2 capsules	1 tablet 2 capsules	0 tablets 3 capsules	0 tablets 3 capsules
800mg/ day	3 tablets 1 capsule	3 tablets 1 capsule	2 tablets 2 capsules	2 tablets 2 capsules	1 tablet 3 capsules	1 tablet 3 capsules	0 tablets 4 capsules

After all tablets have been substituted by capsules, dose may be adjusted if deemed necessary by the physician, to a minimum of 1 and a maximum of 4 capsules. However, a dose decrease should only be chosen if a patient suffers from side-effects. Patients who drop out during this phase due to a lack of effect of amisulpride or olanzapine, may continue into phase III of the study.

Phase III

Those patients who are still not in symptomatic remission after 10 weeks from treatment initiation will continue in an open-label phase in which they will be treated with clozapine. The previous treatment with amisulpride or olanzapine will be gradually tapered off during the first 2 weeks of this phase. Refer to Table 3 for a suggested schedule on tapering off the double blind medication. The left column provides the 4 possible double blind dosages at the end of phase II (1-4 capsules a day); on the respective rows the titration schedule for the first 7 days of phase III are provided. For instance, if a non-responder used 3 capsules a day at the end of phase II, this patient will continue to use 3 capsules a day for the first 4 days of phase III, decrease to 2 capsules a day during days 5-8, decrease to 1 capsule a day on days 9-12, and stop using the double blind capsules on day 13 altogether.

Table 3. Titration schedule capsules end of phase II

Number of double blind capsules in phase II	Day of phase III			
	Days 1 - 4	Days 5 - 8	Days 9 - 12	Day 13
1 capsule	1 capsule	1 capsule	1 capsule	0 capsules
2 capsules	2 capsules	1 capsule	1 capsule	0 capsules
3 capsules	3 capsules	2 capsules	1 capsule	0 capsules
4 capsules	3 capsules	2 capsules	1 capsule	0 capsules

Clozapine will be started at a test dosage of 12.5 mg/day on day 1, 25mg/day on day 2 and 3, 50 mg/day on day 4 and 5, and 75 mg on day 6 and 7. In the second week, dose will be increased daily by 25 mg until a target dose of 400mg/day is reached at day 20 (see titration schedule in table 4 below). Titration can be slowed or stopped below the target dose if subjects can not tolerate the standard titration schedule because of adverse effects. The target dose is 400mg, but can be adjusted to a lower

dose if a patient develops serious side effects. In addition, if a patient fails to respond and side effects are minor, the dose can be increased. In all cases, patient should reach a dose between 100 and 900mg/day at day 20 of Phase III.

Table 4. Titration schedule clozapine (phase III)

Day	Clozapine dosage / day
1	12.5 mg
2	25 mg
3	25 mg
4	50 mg
5	50 mg
6	75 mg
7	75 mg
8	100 mg
9	125 mg
10	150 mg
11	175 mg
12	200 mg
13	225 mg
14	250 mg
15	275 mg
16	300 mg
17	325 mg
18	350 mg
19	375 mg
20	400 mg

The blood level of clozapine (and n-desmethylclozapine) will be measured 4 weeks after the start of phase III. If the clozapine level is not between 400-1000ng/ml (Kane et al., 1988) *and* patients have not obtained remission criteria, dose should be adjusted in order to reach blood levels within the described range. If clozapine levels are not within the specified range but the patient meets remission criteria, clozapine dose should not be increased simply to reach the specified range of clozapine blood levels.

In case blood levels are not within the target range of 400-1000 ng/ml at visit 12 and/or the patient is not in remission at visit 16, a second blood sample needs to be drawn at visit 16, to guide therapeutic adjustments. When blood levels are still not within this target range at visit 20 and/or the patient is not in remission at visit 20, a third blood sample needs to be drawn at visit 20. In case a patient has reached remission criteria, clozapine measurements do not need to be repeated.

6.2. Concomitant medication

6.2.1 Non-permissible medication

During the course of phase I, II and III, the use of antipsychotics in addition to the study medication is not permitted.

6.2.2 Concomitant medication

Mood stabilisers, benzodiazepines, antidepressants and anticholinergic medications are allowed but doses per day need to be documented throughout phase I, II and III.

6.3 Treatment after the medication part of the study

At the end of the medication part of the study patients can continue treatment with an antipsychotic of their own choice following a consultation of their treating psychiatrist. In phase I and phase III of the study, medication is open-label and can be continued with the identical drug if chosen so by the patient and the psychiatrist.

In phase II of the study, medication is double-blind. At the end of this phase, it is important for patients meeting remission criteria and investigators to know which treatment was used during phase II, because the patient responded well to this treatment which should therefore be continued. Unblinding patients at the end of phase II is sensitive, as it is not acceptable that the advantages of a double blind study are diminished by the possibility to change previously collected data after the treatment is unblinded. Therefore, a database lock of the eCRF of phase II (and phase I) data will occur per patient before that individual patients' treatment can be unblinded by the central study team, which has read-only access to the eCRF. After this lock, any changes to the collected data can only occur through standardised queries by the data management center, and will be appropriately documented. This procedure, 'unblinding according to protocol', needs to be performed in a very precise manner. As several data completeness checks need to be performed before the unblinding can take place, one week is scheduled in to ensure proper conduct. For this period, patients who meet remission criteria receive 1 week additional double blind medication. Once the treatment is known, they subsequently flow to the psychosocial intervention.

Patients not meeting remission criteria will start tapering off double blind medication at the end of phase II immediately and start clozapine simultaneously. The unblinding of these patients is not urgent and may taken place during phase III once all requirements for the 'unblinding according to protocol' procedure (described above) are fullfiled.

The randomisation table is only known to the drug manufacturer (Piramal), to prevent unintentional unblinding. The procedure for unblinding in this context is explicitly separate from the procedure that needs to be followed for emergency unblinding, where unblinding envelopes are used at the investigation sites. During monitoring visits and at the end of the study, unblinding envelopes are checked and collected to ensure that treatment for each individual patient was blinded throughout the period that the collected data could be adjusted. In case treatment was known, data from that individual patient will be excluded from analyses.

In all cases the decision regarding antipsychotic treatment after the medication study or discontinuation will be made by the treating physician and should be based on routine clinical practice and taking into account the administration of all possible study drugs in the respective phases of the study (i.e. concerning drug-drug-interactions or other safety issues).

7. Investigational product

7.1 Formulation, packaging and labelling

Study medication will be provided by the central pharmacy (Piramal) for Phase I and II, but not for Phase III. except when a different construction is required by local authoritiesFor Phase III clozapine will be prescribed regularly by the treating physician. In centers were regular prescription of study medication is unacceptable, clozapine will also be provided centrally.

For study phase I, a tablet formulation will be used for the administration of the study medication amisulpride. Amisulpride tablets will be provided in packs: per visit, one pack will be dispensed containing sufficient medication for the applicable visit window.

For study phase II, a capsule formulation will be used for the administration of the study medication (either amisulpride or olanzapine tablets), that will have identical appearance to maintain blinding of treatment assignment. Capsules contain either 200 mg amisulpride or 5 mg olanzapine. Capsules will be packed in bottles that contain a sufficient number of capsules of study medication for the applicable visit window. Each bottle will be labelled in the national language according to the national requirements. Labels will at least list study identification (protocol code and abbreviated title), the randomisation number, the quantity of capsules, the capsules' possible contents (type and strength), the expiry date, information on the use of the drug (oral application, dosage regimen), rules for appropriate storage, instructions for return a safety (children's) warning, the study phase and a disclaimer to its use in a clinical trial exclusively.

7.2 Drug accountability

The patient will be provided with sufficient medication until the next dispensing visit, including spare medication to overcome a potential delay until the next visit.

All dispensed study medication will be returned by the patient to the investigator at the next applying visit and new bottles will be handed out in accordance with the study protocol.
Accountability and subject compliance will be assessed by maintaining adequate drug dispensing and return records.

A Drug Dispensing Log must be kept current and should contain the following information:

- the identification of the subject to whom the study medication was dispensed
- the date[s], quantity of the study medication dispensed *to* the subject
- the date[s] and quantity of the study medication returned *by* the subject

This inventory must be available for inspection by the Monitor. All supplies, including partially used or empty containers and the dispensing logs, must be returned at the end of the study.

8. Methods

All protocol procedures and the most relevant study documents are described in detail in the separate Investigator Manual, with all practical information for the correct conduct of this study.

8.1 Randomization of treatment and blinding

Randomisation, blinding and unblinding is described in more detail in the separate Standard Operating Procedure 'Randomisation, blinding and unblinding'.

8.1.1 Randomization

Randomization of study subjects will be performed by a randomization website which has been developed by the Data Management department of the Julius Center, University Medical Center Utrecht, the Netherlands. This website is a password protected online application that has been used for randomization in over 40 studies. It has been developed in VB.Net with access to a SQL Server back end database. The application implements stratification, multiple sites, double blind randomization and the minimization method for randomization. Access to the system (individual username and password) is provided by the Data Management department of the Julius Center.

Non-responders after four weeks of amisulpride treatment will be randomized to double-blind treatment out of two treatment arms (switching to olanzapine OR continuation of amisulpride). Randomization will be stratified according to site and gender.

Patients who do respond after phase I, II or III will be randomized to one of two treatment arms (routine care plus psychosocial intervention OR routine care alone). Randomization will be stratified according to i) phase where remission was reached (I, II or III); ii) substance misuse; iii) specialized first episode clinic or generic clinic.

8.1.2 Unblinding procedures

Unblinding of study medication before the end of phase II may only occur on an individual basis if the information can help treat an (S)AE and for safety reasons. The decision to unblind is at the discretion of the investigator. For this purpose, every medication box used in phase II of the trial will be supplied with a set of 2 sealed envelopes comprising the information on the type of medication stored in the medication box; one set will be send to the investigator site together with the medication while the other set will be send to the central study team. In the case of a medical emergency situation as described below, the envelope can be opened and the treatment assignment of a patient will be unblinded. This patient will be excluded from subsequent statistical analyses.

Emergency unblinding is indicated in the following situations only:

1. unblinding is necessary for the subjects emergency treatment at the investigators discretion
2. unblinding is required by local laws or regulations (in case of SUSAR)

3. the Data Safety Monitoring Board decides that unblinding is necessary for proper study management of the subjects and the overall safety of the other subjects in the study

All patients who are unblinded will be excluded from analyses. Depending on their clinical status, they are welcome to flow to phase III or the Psychosocial Intervention component. When a study site is closed all closed envelopes will be collected and returned to the manufacturer of the study medication. For patients who meet remission criteria at the end of phase II and are unblinded following the ‘unblinding according to protocol procedure’, the emergency unblinding envelopes at the sites remain sealed as the unblinding is performed by the central study team. Opened envelopes will be kept in the Investigator Site File at the center. After closing of the data base every site will be informed about each patient’s assignment to a treatment group.

8.2 Study procedures

8.2.1 Medication part

Study examinations scheduled in the course of the trail are listed in table 5 below:

Table 5: Patient visits and examinations specified per visit for Phase I, II & III

			Week	Informed consent demographics, DUP	In/exclusion criteria	MINI-plus & physical exam	MRI in 200/ 500	MRS in 62/500	Blood sampling**	Randomization	Dispense study medication	weight, abd circ	Height, ECG	PANSS	Remission criteria	PSP / CGI	CDSS / UKU / SWN	Alcohol and drug abuse	Adverse events	Concomitant med	Drug accountability	Leucocytes	Bloodlevels antipsychotics	Clinical judgment diagnosis
Visit 1	Screening		-1 to 0	X	X	X	X	X				X	X											
Visit 2	Phase I	Baseline	0						X		X			X		X	X	X	X	X	X			
Visit 3			1											X		X		X	X	X	X			
Visit 4			*2*								X			X				X	X	X	X			
Visit 5		Last visit phase I	4					X	X	X†	X	X		X	X	X	X	X	X	X	X		X	
	Phase II	Baseline																						
Visit 6			6								X			X		X		X	X	X	X			
Visit 7			8								X			X				X	X	X	X			
Visit 8		Last visit phase II	10					X	X		X	X		X	X	X	X	X	X	X	X		X	
	Phase III	Baseline																						
Visit 9			11																X	X	X	X		
Visit 10			12											X		X		X	X	X	X	X		
Visit 11			13																X	X	X	X		
Visit 12			14											X	X	X	X	X	X	X	X	X	X	
Visit 13			15																X	X	X	X		
Visit 14			16																X	X	X	X		
Visit 15			17																X	X	X	X		
Visit 16			18									X		X	X	X	X	X	X	X	X	X	X*	
Visit 17			19																X	X	X	X		
Visit 18			20																X	X	X	X		
Visit 19			21																X	X	X	X		
Visit 20		Last visit phase III	22						X			X		X	X		X	X	X	X	X	X	X*	
Visit 21	F/u non responder		48									X		X	X					X				
Visit 22			74											X	X									X

† = randomisation to phase II only when patient does not meet remission criteria at visit 5.
* clozapine levels will be tested at visit 16 and/or visit 20 if the clozapine concentration was not within the specified range during the previous test (visit 12 or visit 16, respectively) and/or the patient does not meet remission criteria at visit 16 and/or visit 20. **Blood sampling concerns the blood markers for WP5 in all patients. In addition, if female patients have a history of breast cancer, and/or a first degree relative with a (history of) breast cancer, prolactin levels should be assessed at the local lab, at visit 2 and visit 5.
DUP=duration of untreated psychosis; abd circ= abdominal circumference; MINI= Mini-International Neuropsychiatric Interview; MRI=Magnetic Resonance Imaging; MRS=Magnetic Resonance Spectroscopy; ECG=Electrocardiogram; PANSS=Positive and Negative Syndrome Scale; PSP= Personal and Social Performance scale; CGI=Clinical Global Impression; CDSS=Calgary Depression Rating Scale for Schizophrenia; SWN=Subjective Well-being under Neuroleptics; UKU= Udvalg for Kliniske undersogelser Side Effect Rating Scale.

Screening

Patients will be screened for eligibility to the study, after informed consent is completed. Potentially existing contraindications concerning the use of any of the study drugs will to be ruled out prior to starting antipsychotic treatment in the study. Diagnosis will be checked using the MINI plus interview. Physical health will be checked in a physical examination. Several demographical and clinical variables will be assessed, including date of birth, sex, educational level, handedness, prior psychiatric disorders and duration of untreated psychosis. In specific centers, MRI and MRS measurements will take place. All female patients are asked whether they have a history of breast cancer, and/or a first degree relative with (a history) of breast cancer. All female patients are counselled on the importance of a routine breast (self)examinations.

So the screening phase serves the dual purpose of conducting or completing such examinations and, if necessary, gradually reducing medication which may no longer be administered after treatment start with study medication. The screening phase preferably does not exceed 1 week in duration.

Baseline examination

At baseline, blood samples will be taken and substance abuse will be measured. If female patients indicated at screening that they have a history of breast cancer and/or a first degree relative with (a history of) breast cancer, prolactine levels are assessed through the local lab at this baseline visit (visit 2) and at visit 5. Management of any prolactin values exceeding the local reference ranges is in line with normal daily practice and at the discretion of the investigator. The amount of blood required for this assessment differs per local lab. The use of concomitant medication and medical conditions/adverse events will be recorded, and study medication will be dispensed for the first time. In addition, the standard rating scales will be used for the first time, including PANSS, CGI, PSP, CDSS and the UKU (see below for details of these scales).

Visits phase I, II and III

Visits 6 until and including 22 (phase II, III and follow-up) will only apply when patients are NOT in symptomatic remission. All patients leaving the study early, regardless of the reason, will be requested to return to the site for one final visit, which will consist of all procedures that were scheduled for the upcoming visit. If the patient is not willing to participate in all this procedures, they will be requested to at least participate in the PANSS assessment.

There is some flexibility in the visit window intervals in phases I, II and III. Visits can be performed with a range of +/- 3 working days. However, regardless of the extend of the deviation in individual visits intervals (as described here) it is essential that the completion of the complete phases fall within a certain interval. That is, it is very important that:

- all patients complete phase I (visit 2, 3, 4 and 5) within 28 (minimum) to 40 days (maximum).
- all patients complete phase II within 5 weeks (minimum) to 7 weeks (maximum)
- all patients complete phase III within 11 weeks (minimum) to 14 weeks (maximum).

Follow-up visits
Follow-up visits are scheduled after the pharmacotherapy phase is completed or when a patient is discontinued, to assess the current status of the patient after that part of the study; one follow-up visit is specifically intended for patient that did not meet remission criteria during phase III, and a second follow-up visit is intended for all patients that have entered phase I. During the final follow-up visit, investigators are requested to provide the most recent clinical diagnosis of the patient.

Rating scales
- Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987): this is a 30-item rating scale designed to measure severity of psychopathology in adult patients with schizophrenia. Five components have been reported: positive, negative, depression, agitation-excitement, and disorganisation. Symptomatic remission will be defined according to the criteria of Andreasen et al. (2005): 8 specific symptoms (PANSS items P1, P2, P3, N1, N4, N6, G5 and G9) of schizophrenia are at the most only mildly present (maximum rating of “3”) so that they do not interfere with daily life functioning.
- Clinical Global Impression Scale (CGI; Guy 1976). Two 7 point scales are used, one for present state, the CGI Severity and another for change, the CGI Improvement scale.
- Personal and Social Performance scale (PSP), a clinician-reported measure of severity of personal and social dysfunction
- Calgary Depression Rating Scale for Schizophrenia. (CDSS) (Addington et al. 1992). This scale is designed to assess depression in patients with schizophrenia without overlap with negative symptoms and extrapyramidal symptoms.
- The Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale for side-effects of anti-psychotic medicationextrapyramidal syndromes: this scale is designed to assess the more common side effects associated with anti-psychotic treatment (Lingjaerde et al. 1987).
- Subjective Wellbeing under Neuroleptics (SWN): self assessment scale of the subjective experience of patients during treatment with neuroleptics (De Haan et al., 2002)

An investigators meeting will be arranged for the introduction of the study protocol and corresponding training in the use of these scales.

Proper conduction of the PANSS interview, the instrument used to measure the primary study outcome, will be taught using instructional videos and checked via the assessment of a test video. Participants in this training will provide information on their experience in using the PANSS through a questionnaire. The number of raters per study site will be limited. Participants whose individual assessment differs by more than 1 point from the master rating on any individual item of the PANSS scale will be re-trained on the relevant assessment criteria. All raters will go through online re-training after 12 and 24 months to refresh training under identical circumstances. All other scales will also be introduced and discussed in their relevance and administration during the investigators meeting.

Additional measures
Weight will be measured at the start and end of each phase during study visits. In addition, abdominal and hip circumference, height and body mass index (BMI) will be noted. An electrocardiogram (ECG) will be performed at baseline. Recreational use

of psychoactive substance use will be recorded. Frequency and quantity of use of alcohol and cannabis will be scored. For other psychoactive substances only frequency will be scored.
At each visit, the presence of adverse events is evaluated. During phase III, the adverse events that are most likely to occur with clozapine are explicitly checked: somnolence, dizziness, tachycardia, hypertension, postural hypotension, constipation, hypersalivation, weight gain, nausea, vomiting, syncope, incontinence at night and blurred vision.

Blood samples
Blood samples for the prediction of treatment response from biological markers will be drawn at baseline (week 0), at the last visit of phase I (week 4), at the last visit of phase II (week 10) and at the last visit of Phase III (week 22) of the medication study. Each blood draw for the biological markers analyses will consist of 50.5 ml, divided over 7 tubes. In case not all tubes can be filled for whatever reason (e.g., objections from the local ERB, patient wants to stop the blood draw, not enough blood can be drawn, etc) it is preferred to leave out 1 STII tube and/or 1 PAXgene tube. This way, at least 1 STII tube and and least 1 PAXgene yube is collected. Leaving both tubes out decrease the amount of blood drawn to 39 ml. Blood count is assessed through local lab, at each blood marker blood draw, in support of the epigenetic analyses (the required amount for this standard assessment differs per local lab).

At the end of phase I and II, together with the samples for biological markers, 1 ml extra blood will be drawn in order to determine the concentration of the antipsychotic used. This measurement provides a reliable indication of the treatment compliance of individual patients, although high-metabolisers of antipsychotics may (seldomly) be included. Samples during phase I and II need to be centrifuged and the supernatant should be frozen immediately (-20 degrees Celsius) and subsequently can be shipped up to one year after the sample was drawn.

In phase III, clozapine blood levels will be measured at 4 weeks after start of clozapine treatment (visit 12). These values will be used to adjust individual doses of clozapine. Target blood levels should be between 400 and 1000 ng/ml (Schulte 2003; Kane et al., 1988). In case blood levels are not within this target range at visit 12 and/or the patient is not in remission at visit 16, a second blood sample needs to be drawn to guide therapeutic adjustments at visit 16. When blood levels are still not within this target range at visit 20 and/or the patient is not in remission at visit 20, a third blood sample need to be drawn at visit 20. As clozapine concentrations are used for therapeutic guidance, samples need to be shipped immediately after they are drawn (room temperature). Additionally, in line with standard practice guidelines for clozapine use, leucocytes will be measured weekly during phase III. For patients using clozapine, leucocyte checks need to be continued for at least 4 weeks when a patient discontinues clozapine. For patients who remain on clozapine therapy, leucocyte counts should be continued weekly until 18 weeks after the start of phase III and thereafter on a monthly base.

8.2.2 Psychosocial intervention

All patients that have reached symptomatic remission as defined by the Andreasen et al. (2005) criteria will be randomized to either treatment as usual, or an additional

psycho-social intervention aimed to increase adherence to medication. In addition, patients who drop out during the pharmacotherapeutic component or who are not in remission at the end of phase III may also be randomized within this study component. There is a maximum of 1 week between the last visit of the medication component of this study and the baseline visit of the psychosocial intervention. In case patients are entering the psychosocial intervention from phase II, medication needs to be unblinded as described in section 6.3 (Treatment after the medication part of the study). This procedure takes up to 1 week. During this time, the baseline visit for the psychosocial intervention can take place. However, unblinding needs to be completed before visit 1 can take place. The baselinevisit for this study component can be planned directly subsequent to visit 8, but no later than 1 week after visit 8. Therefore, the minimum period between visit 8 of phase II and visit 1 of the psychosocial intervention is the time needed to unblind according to the applicable procedures and perform the baseline visit, whereas the maximum period is 2 weeks (one week from visit 8 phase II to baseline visit, and 1 week between baseline visit and visit 1).

The visit schedule is provided in table 6 below.

Table 6: Patient visits and examinations specified per visit for the Psychosocial intervention vs treatment as usual

	Week	Randomi-sation	MI*	weight, abd circ	PANSS	Training on sms & website use*	Adverse event	Con-comitant medication	SOFAS, KPI, DAI, EQ-5D, SCS , Kemp	CALPAS**
Baseline visit	**-1 to 0**	X				X†			X	
Visit 1	**1**		X			X†				
Visit 2	**2**		X		X#					
Visit 3	**3**		X							
Visit 4	**4**		X							
Visit 5	**5**		X							
Visit 6	**6**		X	X	X		X	X		X
Visit 7	**12**			X	X		X	X	X	
Visit 7.1‡	**18**				X					
Visit 8	**52**			X	X		X	X	X	

MI=motivational Interviewing. SOFAS=Global Assessment of Functioning Scale; KPI= Knowledge about Psychosis Inventory; DAI=Drug Attitude Inventory; EQ-5D=Euroqol quality of life scale; SCS=Sellwood Compliance Scale; CALPAS=Therapeutic Alliance Measure

* only for patients randomised to Psychosocial intervention; ** only for patients randomised to Psychosocial intervention, to be given to patient at the end of therapy by the therapist, and returned to the therapist in a sealed envelope.

† these instructions will be provided as soon as possible following randomisation, during min. 2 to max. 4 sessions. Study personnel remains available during the study for additional questions. Additional PANSS assessments are included for specified patients, to facilitate a direct comparison between patients at exactly 22 weeks after start of the study:

only for patients who transferred from phase III; ‡ only for patients who transferred directly from phase I.

Rating scales

- Global Assessment of Functioning Scale symptoms and disability (SOFAS) subscales: administered by doctor or nurse on basis of several sources.
- Knowledge about Psychosis Inventory (KPI) (Barrowclough et al. 1987)
- Drug Attitude Inventory (DAI)
- EQ-5D ("Euroqol") 5-item health related quality of life scale
- Sellwood Compliance Scale (SCS)(Sellwood et al. 2003)
- CALPAS Therapeutic Alliance Measure; self assessment scale for patients
- Kemp scale (Kemp at al., 1998)

The intervention consists of the following three elements.

1. **Web-based psychoeducation**

Psycho-education, especially with family involvement, has been shown to increase adherence with medication in meta-analyses amongst chronic patients with schizophrenia (Pekkala and Merinda, 2005). This intervention is particularly relevant following first episode psychosis, where response to acute treatment and subsequent remission is usually good. Data from Nordentoft's OPUS trial indicated that a comprehensive intervention systematically involving family members increased adherence with medication at one- and two-years follow-up (Petersen 2005, le Quach 2008), and this increased adherence with medication in the experimental condition partially, but not totally explained the positive effect of the experimental intervention on psychotic symptoms.

Psychoeducation in this study will be web-based.The home page of the website will include buttons to take the viewer to the relevant country/language page. Access to the website will be restricted by password login to participants (and their relatives) randomly allocated to the experimental treatment arm. A facility for secure on-line submissions of Q&A will be included. At baseline, participants will be given the option to select a hard copy version of the website as a manual.
The website will be constructed by the IT team in Manchester and hosted on a University of Manchester server under a specific domain name. The content of the website will be drafted by: Dr. Shôn Lewis, Dr. Richard Drake, Dr. Gillian Haddock, Dr. John Ainsworth (from University of Manchester) and by Dr. Merete Nordentoft (University of Copenhagen) and Dr. Peter Jones (University of Cambridge). The website will focus on first episode psychosis, outlining the nature of the disorder, symptoms, outcomes and treatment approaches, with an emphasis on the pros and cons of antipsychotic medication and the importance of maintenance during first remission. The content will be drafted with the input of patients and carers. Two facilitated panels of patients in Manchester and Copenhagen with diagnoses of schizophrenia, will be involved. Family members from each site will also be included. The website will then be translated with patient and relative input encouraged, and locally-specific details added. The final content will be translated locally by the research team, or centrally by EU support if available. Backtranslation will not be required. The final text will then be uploaded to the website. A website counter will count the number of times the participant/family access the site.

2. **Motivational interviewing**

Motivational interviewing will be used as an important part of the psychosocial intervention. Motivational interviewing was developed to help people stop smoking or drinking by eliciting their own motivation for change [Miller, 1983;Miller and Rollnick, 1991]. Important elements in motivational interviewing are analyses of advantages and drawbacks of continued abuse, instruction in coping skills in relation to craving and situations that usually trigger abuse and development of personal strategies for avoiding or handling these situations. In programmes offering help to behavioural changes, analyses of the change process is often used. The circle of change [Prochaska, 1991;Prochaska and Diclemente, 1992] describes changes in behaviour as a process that runs through phases of pre-contemplation, contemplation, preparation, starting, and maintenance.

Although adherence to medication is a different issue, some of the elements described in motivational interviewing can be transferred to this area. Motivational interviewing includes collaborative techniques to facilitate making links between the problems or life goals of importance to the patient and drug treatment, and hence increase their awareness of the importance of adherence if they are to make progress in the areas of their life they hold of value. Most important is the acknowledgement of the patients own thoughts and experiences with medication. It is crucial to get knowledge about which reasons the patients consider important for taking or not taking medication. Therefore it is necessary to create an atmosphere in which the patients feel they can state their opinions frankly. The goal is to elicit the patient's own wish to get help from medication and this can only be achieved if patients are allowed to express also their mistrust and bad experiences, and they should get a clear experience of their concerns being listened to and taken seriously. The sessions aim to help the patient decide how best to weigh up the advantages and disadvantages of taking medication.

As part of the intervention, relatives will be invited to participate in sessions together with the patients and they will be informed about the principles behind motivational interviewing in order to help them to adopt some of the same principles in their contact with the patients.

A standardised motivational interviewing package will be developed. The elements included in the package are information about effects and adverse effects of medication, open discussions about advantages and disadvantages with medication, discussions about the role of medication in the process of remission and recovery, identifying barriers for taking medication and exploration of possibly helpful procedures for remembering to take medication at a given time during the day, related to their routines. The process must include a possibility of acknowledging that although patients have accepted to participate in a drug trial, the patient's perceptions of adverse effects can be of such serious nature that changing medication will be a relevant alternative. This process will be manualised and put on the study website. Training of doctors/ nurses will take place during a 2-day training session. Training and supervision for all doctors / nurses will be performed by the psychology postholder at Copenhagen, supervised initially by professors Nordentoft and Haddock. The researchers that provide the psycho-social intervention cannot also obtain clinical evaluations, as the clinical rater should be blind to whether the patient receives this intervention or treatment as usual.

The motivational interviewing sessions will take place weekly for the first six weeks after randomization. The sessions will last one hour and can be in patients home or the mental health team base, whichever the patient will prefer. The patient's relatives are encouraged to participate in the programme as well. A web-based fidelity checklist will be constructed and completed by all nurses / doctors after the first and last session with each participant.

3. Mobile phone adherence management

There will be two main components to this: SMS medication reminders and real-time symptom and side effect assessment over een period of 1 year. A central secure server at the University of Manchester will be used for the medication management programme. This will involve a web page on the prescribers' website (see above) where details of the prescribed medication schedule for each participant enrolled will be entered locally by the doctor or nurse within two days of randomisation. SMS message alerts, whose content has been agreed with the individual participant, will be sent daily or twice daily to the participant's mobile phone according to their medication schedule. The message will be modifiable, regarding content as well as frequency/timing, by clinician and participant.

In addition a web interface will be constructed to be held on the central server to allow participants to be cued by SMS to enter simple data on levels of symptoms and side effects. The level of detail will be limited by the screen size and time considerations and will be finalised during the beta testing phase. It is likely to consist of a maximum of four questions each on symptoms and side effects with a four-level (none-mild-moderate-severe) response field, taking no more than two minutes to complete. The responses will be wirelessly uploaded automatically to the server with full privacy and security. Summary details will be made available to the clinical team each week with the participants' initial consent. Participants will be given two twenty minute training sessions alongside the psychoeducation sessions. Participants will twice weekly be prompted by SMS to complete the ratings. The system will be beta-tested (field trialled) in eight patients from Manchester and Copenhagen, with the option of 1-2 patients from each participating site.

Detailed arrangements for deploying the system via local service providers will be established through links with the new m-Health Innovation Centre at the University of Manchester in association with GSMA (www.gsmworld.com). GSMA aims to establish a network of mobile health (m-Health) Innovation Centres across the world, providing support and infrastructure for m-Health research, innovation and commercialisation of new m-Health services. In October 2009, GSMA established Manchester as the first of these Centres. A major focus of the centre is the area of Assisted Living (included mental health). The deployment of enabled handsets for the Optimise trial across different EU sites is one of the first partnership tasks to be adopted by the Manchester m-health innovation centre.

Participant assessments

Baseline measures, assessed at the start of the psycho-social intervention study will be as follows:

Participant

1. Global Assessment of Functioning Scale symptoms and disability (SOFAS) subscales: administered by doctor or nurse on basis of several sources. 2 minutes of participant time.
2. Knowledge about Psychosis Inventory (KPI) (Barrowclough et al. 1987) (10 minutes)
3. Drug Attitude Inventory (DAI)(10 minutes)
4. EQ-5D ("Euroqol") 5-item health related quality of life scale (5 minutes)
5. Sellwood Compliance Scale (Sellwood et al., 2003; 1 minute)

Prescribing clinician
Kemp compliance scale (Kemp et al., 1998).
Casenotes and clinician

1. Relapse
2. Rehospitalisation

All of these scales will be re-administered at 3 and 12 months post-randomisation by an independent assessor who will be blind to treatment allocation. Blindness will be maintained by a range of measures including geographical separation of raters and password protected databases.

At the end of the 6 weeks series of motivational interviewing sessions, the CALPAS Therapeutic Alliance Measure will be completed by the patient.

Following randomisation, participants and, where possible, family members in the experimental treatment arms will meet with the research nurse on two (or up to four if needed) occasions either at home or at the clinic to learn how to (i) access and navigate the psychoeducation website and (ii) operate the SMS and mobile phone interface and complete the rating scales. Thereafter, the research nurse will be available to discuss issues arising out of the website material.

8.2.3 MRI measurement

A separate protocol describes the MRI and MRS measurements that are included in detail. Below basic information on this study component is provided.

Site requirements
Each site must have access to an MRI scanner, preferably, but not necessarily 3T. 1.5T scanners may also be used.
Volumetric imaging data will be acquired using the ADNI protocols. These have been specifically developed for multi-centre imaging studies, and can be run on most recent scanners from Siemens, Phillips, and GE. The WP leader centre (IOP) already has experience in successfully implementing this protocol in another multi-centre MRI study funded by the EU to assess brain processes related to addiction in a sample of 2000 subjects (FP6; I MAGEN).

Each MRI site will be assisted by our subcontractor IXICO (www.ixico.com), a company that specializes in MRI data handling in multi-centre studies. This will help to ensure quality control, and appropriate data collection and data transfer. The data will be stored centrally by IXICO in London. Both the radiological assessments and the MRI data analysis will be performed at the Institute of Psychiatry in London.

Image acquisition
The scanning sequences are not complicated and the scanning session is likely to take about 45 minutes in total. Data will be acquired using standard localiser ('scout') images, followed by 2D T2-weighted and FLAIR scans on different planes with parameters suitable for radiological assessment. Scan times for these sequences will differ slightly between scanner manufacturers, but should total less than 10 minutes at all sites. This will be followed by a 3D ('volumetric)' T1-weighted MP-RAGE scan, based on the protocol devised and validated by the ADNI consortium.112 This will take a further 9½ minutes. Data will be archived by each site according to existing local procedures, and will also be transferred (using the DICOM protocol supported by all scanners) to a project-specific computer, where, following basic consistency checks, it will be anonymised for transfer to the central coordinating/analysis site using the IXICO software (which will be provided to all sites).

Collation of MRI data at central coordinating site
MRI data plus associated demographic data from each site will be transferred from the LDC at each site to a central computer system. Data transfer and management will be conducted in collaboration with SME IXICO (www.ixico.com) to ensure efficient dataflow, auditing and central quality control. IXICO has a wealth of experience running multi-centre MRI studies worldwide.

Standardisation of data quality across sites
To ensure high quality data, standard QA protocols (using the ACR MRI phantom) will be run at regular intervals (monthly) at all sites. Data will be analyzed locally (to allow a rapid 'turn round' if any issue is uncovered requiring servicing of the scanner), and also transferred to the central analysis site, where they will also provide information for inter -site calibration of voxel sizes.

A group of healthy volunteers (n=5) will be scanned at a subgroup comprising the largest participating sites using the standardised acquisition protocol. This will establish the comparability of the MRI data across centres, and provide measures of within- and between- scanner variability.

Data analysis
Radiological assessments will be performed at the coordinating site for MRI assessments (Institute of Psychiatry, King's College Londen) by one of two experienced neuroradiologists who are blind to the nature and purpose of the study. Using software provided by IXICO, they will assess all MRI images for any abnormalities as they would in conventional clinical practice, and will be asked to specify whether abnormalities require clinical action. They will be blind to whether subjects are patients or controls. The neuroradiological evaluation will assess:

a) Absence or presence, location and number of lesions scored on a scale of 0 to 3 (0=none; 1=single lesion; 2 more than one lesion in the same hemisphere; 3=more than one lesion in both hemispheres)
b) The ventricular system size and shape; Subarachnoid spaces and basal cisterns. Size will be reported on a scale of 0 to 1 (0=normal; 1=enlarged).
c) Septum Pellucidum and its variants will be scored from 0 to 3 (0=normal; Cavum Septi Pellucidi=1; Cavum Vergae=2; Cavum Veli Interpositi=3)
d) A whole brain gradient (anterior-posterior) and asymmetry (left-right) atrophy visual evaluation will be made in order to assess absence or presence and type of atrophy: overall proportional atrophy, cerebral convexity only, widened

Sylvian fissure, focal atrophy. Frontal and parietal lobes will be rated on a scale from 0 to 4 (0=none; 1=minimal; 2=mild; 3=moderate; 4=severe). Four regions of the temporal lobes will be investigated as proposed by Galton: hippocampus, amygdala, fusiform gyrus and parahyppocampal gyrus on a scale from 0 to 4 (0=none; 1=minimal; 2=mild; 3=moderate; 4=severe)

e) Absence or presence, location and characteristics of signal intensity abnormalities. Lesions will be scored on a rating scale from 0 to 6, as proposed by Scheltens with separate scores for each of the cerebral lobes, the periventricular, the subcortical regions, and the infratentorial brain structures. Perivascular spaces will be disregarded.
f) Height, width, and anteroposterior diameter of the pituitary gland will be reported together with morphological characteristics of the pituitary stalk.

Measurements and ratings will provide data for inter-rater reliability calculations.

8.3 Withdrawal of individual subjects, premature termination of the study

There are several reasons which may lead to prematurely terminatation of a patient's participation, a study center's contribution to the trial, or a complete cessation of the whole trial. These reasons are indicated below.
Reasons to terminate a patient's participation:

- The patient withdraws her/his consent
- Intolerance to the study drug
- The nature of the patients treatment is changed to coercive treatment (based on judicial ruling)
- In contrast to the patient's status at enrollment, the patient is now represented by a legal guardian or under legal custody
- Emergence of one or more contraindications against any of the study drugs as mentioned in the Summaries of Product Characterics (refer to Appendix A). In particular, clozapine use needs to be discontinued when one or more of the following adverse events occur: severe leucopenia (leucocyte count <3000/mm^3 or 3.0x10^9/l) or neutropenia (count <1500/mm^3 or 1.5x10^9/l), myocarditis or cardiac arrhythmias.
- Patient becomes pregnant or initiates lactation
- The investigator considers a patient's continued participation in the study to be unjustifiable on medical grounds (i.e., because of side effects or unusual risks).

If an individual patient is discontinued due to one of the above mentioned reasons, this patient will be treated as usual in normal daily practice.

Study center:

- Inability to conduct the study in accordance with protocol at a particular study site, inability to maintain agreements made with the study sponsor, or inability to meet ICH-GCP guidelines
- Insufficient inclusions, i.e. < 5 patients included per year

If a study center discontinues the study on behalf of one of the above mentioned reasons. The patients that have already been included will be followed up, but no new inclusions will be made.

Study:

- The approval conditions or risk profile of study medication amisulpride, clozapine or olanzapine changes, making a new assessment of the use of these drugs in this study necessary

In case the entire study is discontinued, patient will followed-up and/or be treated as usual in normal daily practice, depending on the severity of the changes in risk profile and the extent to which this increase in risk is applicable for individual patients.

All patients leaving the study early, regardless of the reason, will be requested to return to the site for one final visit, which will consist of all procedures that were scheduled for the upcoming visit. If the patient is not willing to participate in all this procedures, they will be requested to at least participate in the PANSS assessment. There are no consequences if a patient also refuses this.

9. Statistical analysis

9.1 Data analysis

Data analysis for objective: Finding evidence for pharmacotherapy guidelines in first episode schizophrenia

The primary outcome will be the number of patients in symptomatic remission according to Andreasen et al. 2005. The proportion of patients meeting remission criteria will be estimated at the end of phase I, phase II, and phase III. Logistic regression analyses will be used to test whether the probability of remission is significantly different between the amisulpride and olanzapine treatment arms at the end of phase II. Duration of untreated psychosis, age, and gender will be included as covariates in this analysis. The secondary outcome measure is all-cause treatment discontinuation, which will also be compared between treatment arms with survival analyses including Cox regression analyses and Kaplan-Meier functions.

Data analysis for objective: Finding biological predictors of treatment response

DNA analysis

DNA will be used to study genetic markers with a pharmaco-genetic (PG) chip developed at INSERM. This PG-chip, which is dedicated to genotyping 15,000 polymorphisms, makes it possible on the one hand to reconstruct the haplotype diversity of 1292 genes implicated in the metabolism, transportation, and targeting of drugs and, on the other hand, to genotype the functional polymorphisms that are indispensable for certain genes which are not included in GWA chips. This is a tool at the intermediate scale between a low-throughput candidate gene approach, and a pan-genomic approach, for which virtually no pharmacogenetic cohort has sufficient power. This PG chip includes genes implicated in: drug metabolism, drug transport, inflammation (including 158 HLA genes), metabolism, apoptosis, inflammation, chemokines, cytokines, brain receptors and other proteins, signal transduction (carcinogenesis), and DNA repair. This PG-chip has come into production early 2009 (Pr Beaune INSERM). DNA will also be used to characterize the methylation profiling before and after treatment with amisulpride. DNA collected before and after treatment will be converted using bisulfite treatment and hybridized on HumanMethylation27 BeadChips on Illumina platform (Integragen). These BeadChips contain 27,578 CpG islands spanning more than 14,000 genes. Methylation data analysis will be analysed

using the BeadStudio software, which will allow the integration with gene expression data (Dr Jamain, INSERM).

Metabolomics analysis

Plasma will be portioned and snap-frozen as soon as possible after collection. Plasma (50µL) is required for a single assay. Samples will be processed in a fully automated manner in multiwell plates using Hamilton robotics station. Metabolite spectrum is designed to monitor the metabolism of sugars, acylcarnitines, amino acids, glycerophospholipids, sphingolipids and many other analytes. The resulting dataset will be subject to several levels of data analyses, starting with metabolite identification and quantification based on the raw multiplexed MS/MS spectra and the knowledge of the spiked isotope reference markers. In this step, BIOCRATES Life Sciences MarkerIDQ™ software shall be used as provided with the AbsoluteIDQ™ kit. In a second step, correlations within the metabolite dataset will be combined with external biochemical knowledge (e.g. from metabolic pathway maps, KEGG), using bioinformatics tools developed specifically for every project at HMGU-IBIS.

Proteomics analysis

Plasma will be used to look for proteomic biomarkers of response in 30 responders and 30 non-responders after phase I matched for ethnicity, gender, and age. The discovery phase of the project will focus on the identification of novel specific biomarker patterns relevant to predicting and/or monitoring patient response to amisulpride treatment in serum/plasma. In the discovery phase two-dimensional gel electrophoresis will be used followed by labelled MS based discovery, which is more sensitive than label free methods. Any findings will be validated in the full set of responders and non-responders by direct MS multiple reaction monitoring and immunodetection methods. (Pr Lovestone's and Pr Collier, proteomics laboratory at the Institute of Psychiatry).

MRS analysis

Measurement of glutamatergic function.

MRS spectra (PRESS (Point RESolved Spectroscopy); TE=30ms, TR=3000ms, 96 averages) will be acquired in the anterior cingulate and left thalamus, using an established protocol (Stone et al, 2009). Shimming and water suppression will be optimised, with auto-prescan being performed twice prior to each scan. The anterior cingulate Region of Interest (ROI) will be prescribed from the midline sagittal localiser, and the centre of the 20mm x 20mm x 20mm ROI was placed 13mm above the anterior section of the Genu of Corpus Callosum at 90o to the AC-PC line. A 15mm x 20mm x 20mm (right-left, anterior-posterior, superior-inferior) left thalamus ROI will be defined at the point in the coronal slices where the thalamus is widest, using sagittal and coronal localisers to ensure that the voxel was clear of CSF contamination. After the subject leaves the scanner, each scanning session will conclude with the collection of a PRESS spectrum from a phantom containing standard concentrations of brain metabolites to provide calibration data for the LCModel program. All spectra will be analysed using LCModel version 6.4. This generates water-scaled values. To generate metabolite concentrations, SAGE (General Electric, Milwaukee, USA) will be used to combine data from the 8 channel head coil, which uses unsuppressed water peaks to scaled data from each head coil relative to each other but does not scale the combined signal relative to water. The combined data will then be analysed using the integrated SAGE GUI for LCModels.

Data analysis for objective: Testing the utility of MRI screening

The statistical analysis of the MRI data will use two approaches: 1) A well established volumetric method; 2) Pattern recognition analysis (Support Vector Machine).

The volumetric analysis will use voxel-based morphometry (VBM), as implemented in SPM, the most widely used statistical software package for this purpose. This analysis will be performed at the Institute of Psychiatry, King's College Londen , who were the first to apply this approach in MRI analysis and have extensive experience in its application in schizophrenia.

The pattern recognition analysis will investigate spatially distributed information on brain tissue structure, using multivariate pattern recognition approaches**.** Statistical pattern recognition is concerned with automatic discovery of regularities in data through the use of computer algorithms, and with the use of these regularities to classify the data into different categories. Brain scans are treated as spatial patterns and statistical methods are used to identify statistical properties of the data that discriminate between groups of subjects (e.g. responders vs. non-responders to treatment). This analysis will be performed at the Institute of Psychiatry King's College Londen,by the investigators and their collaborators. The Institute of Psychiatry has pioneered the application of pattern recognition and machine learning methods in psychiatry. To date, most analysis methods used in MRI studies of schizophrenia have sought to distinguish subjects at a group level; this approach permits MRI analysis at the level of the individual patient.

9.2 Drop-out rates and missing values

Fleischhacker and Kemmler (2007) reported an average drop-out rate of 28% in current, double-blind, randomised studies with short treatment duration (up to 12 weeks). This was a registration study performed by the pharmaceutical industry which included active treatment arms only. As the current study will not be conducted using substances that are in the approval phase and phase I is a single-arm, open-label intervention, adding up to expected lower drop-out rates, we based our calculations on a drop-out rate of 20% over the complete course of phase I and II.

Several strategies are planned a priori to deal with missing study data concerning the primary study outcome from patients who aborted treatment:

(a) Reasons for treatment discontinuation will be registered, as this will provide information on the missing data process which may either be Missing at Random (missingness is related to observed variables) or Missing Not at Random (missingness is related to unobserved data (Little & Rubin)
(b) Analysis of the primary study outcome will be done according to the Intention To Treat (ITT) method. In addition multiple imputation using Rubin's propensity score method (Rubin 1987) will be used in its implementation in the software "SOLAS for missing data analysis"(version 3.0).
(c) An additional analysis of study completers who completed the entire study according to protocol will be conducted (protocol analysis)
(d) Baseline characteristics of patients who later dropped out of the study will be compared with those of study completers in the non-switch and the switch groups to identify possible factors influencing later drop-out

(e) Analysis of the primary study outcome will be done according to the ITT method. The last-observation-carried-forward (LOCF) method will be used to deal with missing values
(f) In addition multiple imputation using Rubin's propensity score method (Rubin 1987) will be used in its implementation in the software "SOLAS for missing data analysis"(version 3.0). Here, 5 datasets are created with imputed missing values, resulting in 5 complete datasets
(g) An additional analysis of study completers who completed the entire study according to protocol will be conducted (Per Protocol (PP) analysis)

10. Analysis of risks and benefits

Participants included in the study will have recently experienced a deterioration of their health, exhibit the clinical symptoms of schizophrenia, schizoaffective or a schizophreniform disorder, and hence require an antipsychotic, medication-based treatment. Both types of medication in the study used in phase I and phase II have been licensed for the treatment of schizophrenia in most European countries (with the exception of amisulpride in The Netherlands) for over 10 years and are routinely used in clinical practice. The examinations performed for the study will only marginally stress participants more than routine therapy would.

If the hypothesis that early switching to an alternative antipsychotic featuring a different receptor profile in case of poor initial response is confirmed, a patient who initially experiences little benefit from open-label treatment with amisulpride in phase I of the trial and is switched to the treatment with the alternative antipsychotic drug olanzapine in phase II may have a higher chance of reaching remission by the end of phase II. Nonetheless, patients cannot expect guaranteed individual benefits in phase II of the trial as treatment assignment is randomized and patients in phase II may stay on the identical antipsychotic they were on in phase I of the trial. However, patients are carefully followed up regarding their individual benefit from the treatment in phase I and phase II and are then switched to clozapine in phase III. In routine treatment this extensive monitoring of the treatment effect is not applied and so patients may benefit from the thorough examinations during study participation. Insufficient response cannot be overlooked which is an advantage of study participation compared to routine care.

The OPTiMiSE study's results could indicate a future treatment strategy for patients who initially respond poorly to antipsychotic treatment. This means that the ineffective continuation of treatment of patients with a poor initial response could be prevented. Additionally this would prevent unnecessarily long hospitalizations, reducing the treatment cost of an acute episode since hospitalization costs comprise the largest part of the total cost of therapy.

In the face of the small amount of additional burden to the patient of participation as compared to routine treatment, the possibility of individual benefit, and the possible positive outcome for future treatment, offering participation to selected patients appears to be justified.

11. Feasibility of patient recruitment

Although there are no pilot studies for the current trial, the study design resembles that of many randomised, double-blind approval studies in which patients received antipsychotics. Given that many such studies have already been successfully completed, it seems reasonable to assume that with respect to sample size, the chosen statistical methods, and the estimated number of patients who will drop out, the present study can be realised. The present study will not use any medication which is yet to be approved and does not ask many extra activities of the patients, making recruitment all the easier.

The current study is supposed to be executed in 30 centers and run over a course of five years. This means that the mean number of inclusions per center per year is only 5, which should not be too demanding.

The broadly chosen inclusion and exclusion criteria (which differ markedly from the often very restrictive criteria of approval studies of pharmaceutical companies) allow a higher degree of generalisation of the results and at the same time make recruitment easier. The conducted examinations and treatment in the study only minimally differ from the clinical routine, with the exception of blinding and the randomisations.

Finally, the trial builds on the previous experience with the EUFEST study, which included 498 first episode patients in two years. With a few adjustments, the same centers involved in EUFEST will also participate in OPTIMISE. As the case number in EUFEST (n=498) was reached in two years, the current trial (n=500), the recruitment aim should be reached.

12. Safety reporting

Safety aspects are described in more detail in the separate Standard Operating Procedure ‘Satefy Review and Reporting Procedure’.

12.1 General aspects

This study will be performed according to the Declaration of Helsinki (2008) and the International Conference on Harmonisation - Good Clinical Practice (ICH-GCP)**.** The definitions of adverse events and serious adverse events described in these guidelines will be used for the present study.

All medication to be administered in this study has been used in clinical pratice for the treatment of schizophrenia and schizophreniform disorder in Europe for more than 10 years. Therefore, no special checks are included except the once that are routinely used for clinical treatment using the medication applied in this study.

The investigator will inform the subjects and the reviewing accredited Ethics Committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the Ethics Committee, except insofar as suspension would jeopardise the subjects’ health. The investigator will take care that all subjects are kept informed.

12.2.1 Definitions

Adverse Events (AE) are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational drug.

In case a female participant becomes pregnant during the course of the study, this will be reported as an AE.

A Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose results in:
- death
- is life threatening (at the time of the event)
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention (e.g. medical, surgical) to prevent one of the other serious outcomes as listed above

The following events which may occur during this study, will be regarded as SAEs if they meet the criteria, yet will not need to be reported immediately to the sponsor (UMC Utrecht, the Netherlands), but rather within a time period of 1 month:
-exacerbation or de novo occurrence of schizophrenia symptoms, including positive, negative and cognitive symptoms.
-severe forms of well known and common side effects, such as acute dystonia, severe sedation, epileptic seizures or agranulocytosis, which are rated in the eCRF using a specific rating scale (UKU) and on the applicable adverse event pages.

Hospitalisation due to exacerbation of psychosis-related symptoms is a very common occurrence during the first years of the illness. Although this is regarded as being an SAE, these hospitalisations are part of the illness course and are therefore not reported to the authorities immediately. Rather, they will be reported once a year as part of the Annual Safety Report (section 12.2.4). Immediate reporting will not have any added value for the authorities in evaluating patient's safety and will result in over-reporting.

An event qualifies as a SUSAR when:
- the criteria for an SAE are met
- it is plausible that the event is caused by the study medication
- the event is not expected, based on the 'summary of product characteristics' (that is, it is not a known side effect).

12.2.2 AE, SAE and SUSAR reporting procedures

All AEs reported spontaneously by the subject or observed by the investigator or his staff will be recorded in the patient file and eCRF by the investigator.

Any SAE must be immediately reported to the sponsor (UMC Utrecht, the Netherlands) regardless of their estimated relatedness to the study drug. SAE's

should be reported by filling out the SAE form in the eCRF within 24 hours after the investigator came aware of an SAE. By means of the eCRF an email alert will be send to the UMCUtrecht for report to the regulatory authorities. When the eCRF system does not function, reporting must be performed by facsimile transmission of the completed SAE form to the trial assistant, fax number: +31- 88-7555466.

Should the investigator become aware of an SAE that occurs within 30 days after stopping the study treatment, the SAE must be reported in accordance with procedures specified above. This can be either 30 days after Phase I, Phase II or Phase III, dependent of the number of treatment Phases the individual patient needed to obtain remission criteria.

SUSAR's will be reported using the same procedure as SAE's described above. One important difference is that the patient will be unblinded when the SUSAR occurs during the double blind phase (phase II).

In case an SAE or SUSAR is reported, all other investigator sites will be informed by the central study team with regards to this event. Any information that is needed to adhere to local laws and regulations of participating countries will be provided by the trial co-ordinators and/or the project manager. All SAEs and SUSARs will be reported by the central study team and the investigator site to the appropriate Dutch authorities, in accordance with local laws and regulations. However, SAEs and SUSARs cannot be reported centrally on a European level, so each investigator needs to ensure that local laws and regulations are followed in case an SAE occurs in their centre, that is: the ERB or other national authorities may need notification. All information regarding SAEs, SUSARs and the reporting of these events will be filed in the central study file as well as the investigator site files.

As stated above, hospitalisation due to exacerbation of psychosis-related symptoms, exacerbation or de novo occurrence of schizophrenia symptoms and severe cases of common side effects of antipsychotics that meet SAE criteria, do not need to be *immediately* reported as SAEs in the standard procedure. Hospitalisations due to exacerbation of psychosis-related symptoms will only be reported in the Annual Safety Report (section 12.2.4). Regarding exacerbation or de novo occurrence of schizophrenia symptoms and severe cases of common side effects of antipsychotics that meet SAE criteria; these will need to be reported to the sponsor (UMC Utrecht) within **1 month** of the occurrence of the SAE. ERBs and/or other local authorities may wish to receive a list of the events of hospitalisations, symptom exacerbations and severe common side effects that did meet SAE criteria. This list will be periodically composed and distributed amongst investigative sites, at least once a year, depending on the requests of ERBs and/or other local authorities. The report for the SAEs that can be reported with delayed timelines, can be entered into the eCRF or can be reported through facsimile transmission of the completed SAE form to the trial assistant, fax number: +31- 88-7555466.

Next to this list of hospitalisations and exacerbations, a list of all SAEs and SUSARs will be provided for the appropriate authorities (developed by the central study team, submitted by the investigators), including a summary table arranged on organ systems and a statement of the Data Safety Monitoring Board regarding a cost-benefit evaluation.

12.2.3 Follow-up of adverse events

All adverse events (AE's, SAE's and SUSARs) will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

12.2.4 Annual safety report

Once a year, the central study team develops a list of all SAEs and SUSARs that have occured during the study. This annual safety report will be distributed among all investigator sites, to be submitted to the appropriate local authorities and filed in the investigator study file. This safety report includes a summary table arranged on organ systems. In addition, a statement on the cost-benefit balance for study participants by the Data Safety Monitoring Board is included, based on a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

12.2.5 Data Safety Monitoring Board

The safety of the study will be judged by an independent committee of experts on regular basis, at a frequency of at least once a year. The members of this board will have access to the unblinded data of phase II, to all SAEs and SUSARs and to the inclusion and drop-out rates. This Data Safety Monitoring Board (DSMB) will suggest changes to the protocol or provide an altered judgement of feasibility if information from the annual safety report or new information about the applied study medication has become available.

13. Ethical considerations

13.1 Regulation statement

The study will be conducted in accordance with the principles of the Declaration of Helsinki (59th WMA general assembly; October 2008), with the ICH-GCP guidelines and other applicable (national) laws and regulations. In line with these guidelines, insurance is arranged by the sponsor for all participating sites.
All investigators involved in the present study will receive a copy of the guidelines and important points will be discussed at the investigators meeting at the beginning of the study and in detail during site initiation.
Every investigator involved in the study is responsible for compliance with protocol, compliance with ICH-GCP guidelines and other existing laws and regulations.

13.2 Statement regarding ethical practicability of the current study

All patients will receive open-label amisulpride treatment for 4 weeks. Subsequently patients with a poor response to treatment will either continue the treatment with the identical drug (amisulpride) or switch to the alternative study drug (olanzapine). Since current treatment guidelines for schizophrenia therapy recommend continuing

medical treatment for 4 to 8 weeks, the total treatment length of 10 weeks in the case of a continuation of the initially started study drug amisulpride will only slightly exceed these recommendations.
Both study drugs have been approved in most countries for the treatment of schizophrenia for over 10 years, so that no significantly higher medical risk arises from participation compared to routine treatment with amisulpride or olanzapine, with the exception of the double-blind study conditions and the randomised assignment of medication.
According to the study's hypothesis, patients with poor initial response to treatment would improve their chances of reaching remission if they were assigned to the alternative treatment arm (olanzapine) in phase II of the trial. This may represent a potential benefit of the study.
There is consensus that clozapine is the most effective antipsychotic drug available. There is a concern about the possibility of agranulocytosis in approximately 1% of the treated individuals. This risk must be balanced with the considerable percentage of patients, who do not respond to first, or even second line treatments. The treatment algorithms are quite explicit about what to do next – switch to clozapine, as is the case in OPTIMISE. The problem of agranulocytosis will be controlled by weekly blood-counts. In addition, the clozapine part of the trial is open label, allowing to closely monitor side-effects and to intervene immediately.
The study is preceded by a thorough informational discussion with a doctor, during which the patient will be informed about every aspect of the course of the study, the potential individual benefits, and the personal risk. Participation is only possible after submission of written consent, whichcan be revoked at any time without citing reasons.
Every participant receives a study number. Data on participation is recorded in a pseudonymous way, i.e., the study site passes on, stores, and analyses the data and study results without stating the participants' name or address. Merely the study site could match a study participant to his or her personal data via the patient identification list in case of emergency.

14. Independent ethical committees, informed consent procedure and data privacy

14.1 Submission to independent ethical committees

Before study start the principal investigator of each participating site will submit a complete set of relevant documentation to the respective independent ethics committee for approval according to the national / local regulations data.
The study will only begin when all documents have been evaluated by the ethics committee and have been accepted without reservations. A written confirmation of the unreserved acceptance of the proposal under consideration of the presented documents must be present.
Over the study's course, the principal investigator of each participating site is also responsible for informing the ethics committee on the progress of the study and changes in the protocol or other study-related documentation according to the local regulations.

14.2 Informed consent

Participation in the study is preceded by a thorough counselling by a doctor in accordance with the Declaration of Helsinki and with ICH-GCP guidelines, during which the patient must be informed about the entire course of the study, potential individual benefits and personal risk. Here it must be re-emphasized that participation is absolutely voluntary, and treatment alternatives aside the present study must be explained to the patient. Patients are given sufficient time to read all the provided information, counsel partners or relatives, and clarify any questions with the investigator.
Regarding data privacy, patients will be informed about pseudonymous recording and sharing of data in accordance with the requirements for documentation and information. In case patients cannot agree to this passing on of data they cannot participate in the study.
Participation only becomes possible after handing in written consent. This consent can be revoked at any time without citing reasons. No examinations or other activities will take place before the participant has handed in written consent to participate.
A copy of the consent form and patient information will be given to the participant along with a copy of the insurance certificate for study participants.
In case patient information or the consent form change, participants will be informed immediately and relevant information will be passed on to the ethic committees for approval. New patient information and consent will be discussed in detail again, the participant will again be asked for written consent, and a copy of the documents will be given to the patient.

14.3 Data privacy

Privacy laws and regulations will be adhered to during all phases and procedures related to this study. The collection and processing of participants' personal information will be limited to what is necessary to insure the study's scientific practicability, the evaluation of efficacy, adherence, side-effects and the treatment's safety. Information collected about participants during this clinical investigation will be treated confidentially. The local investigator or her/his co-workers will collect data and transfer it without recording the patient's name or date of birth coded with a patient identification number.

Pseudonymous data will be relayed to the study center for scientific analysis or made available, if necessary, to the responsible federal supervisory authority (in case it audits the course of the study). Only qualified and authorised collaborators of the study sponsor will enter the pseudonymous data into a computerised database.
The acquired data will be used without participants' names for scientific analysis and can be used in related or other future studies. Participants' names will not be mentioned in any publication of study results.
To ensure data accuracy, the study coordinator will conduct a direct comparison of the data with medical records available to or assembled by the investigators at the study site. These documents will only be checked by qualified and authorised personnel. Persons monitoring the data are required to keep information confidential and to respect data privacy.
Participants have the right to look into their data and can check their data in accordance with the relevant judicial regulations and procedures.

15. Study administration

15.1 Changes in protocol

Changes to the protocol will be documented in a protocol amendment and submitted to the Ethics Committees and, if necessary, National Authorities according to the regulations.

15.2 Study registration

Before the start of the study all required documents will be submitted to the responsible Ethics Committees and regulatory authorities. The study is registered as an interventional study at the European center for clinical studies (EudraCT). Furthermore, the study will also be registered on the website "www.ClinicalTrials.gov"of the American Department of Health, a data base for clinical studies conducted world-wide.

15.3 Documentation of study results

Local investigators will enter the acquired data and examination results into an electronic case record form (eCRF) that is accessible via the internet. Investigators will receive personal user names and passwords for this purpose, and data will be encrypted for transfer. For each site, it will be agreed before the start of the study which documents serve as source documents for all data entered into the eCRF.

The investigator must (electronically) sign that entries into the eCRF are true and complete.

15.4 Quality control of data acquisition

Study sites and associated investigators will be carefully selected and comprehensively informed and trained regarding Good Clinical Practice (GCP), all study procedures and the required examinations and documentation.

The quality of data acquisition will be ensured by regular monitoring visits. After data have been submitted to the study center, another thorough inspection of the completeness and plausibility of entries will be conducted. If needed, questions for clarification will be addressed to the sites. Only after all questions regarding data quality have been answered, the database will be locked (data-lock).

15.5 Archiving of study documents

In accordance with national laws and guidelines and the specifications of the ICH-GCP guidelines, the investigators from participating sites and the coordinating center are obligated to archive all documents pertaining to the study for 15 years after the last patient has completed or discontinued from the study.

15.6 Monitoring

Monitoring will be performed by a CRA from the central study team, UMC Utrecht, The Netherlands according to national laws and guidelines and the specifications of the ICH-GCP guidelines. Details will be documented in a separate monitoring plan. Study monitors will visit study sites at regular intervals to monitor the execution of the study. Monitors will have access to all documents that are needed to perform their task according to the above mentioned guidelines. Monitors will check whether requirements to conduct the study are met and study procedures are followed correctly, and will check the study site's documentation, the participants' source data, eCRF entries, and the correct maintenance of the Investigator Site File.

15.7 Audits

The study sponsor or responsible regulatory authorities can audit, i.e., thoroughly investigate a study site at any time. In this case, auditors are to be given access to all documents relevant to the study and its correct execution.

16. References

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Appendix A

INVESTIGATOR'S SIGNATURE SHEET FOR PROTOCOL

Protocol No.: KP7 242114 **Protocol Title**: Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) Version 2.4 dated July 6, 2015	

I agree to the conditions relating to this study as set out in the above named Protocol. I fully understand that any changes instituted by the Investigator(s) without previous discussion with the appropriate sponsor personnel would constitute a violation of the protocol, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the well–being of the subjects).

I acknowledge that I have read the above named Protocol and agree to carry out all of its terms in accordance with applicable regulations and law, to follow ICH GCP guidelines for good clinical practice, to obtain approval from the IRB / IEC prior to implementation, to allow direct access to source documents, and agree to inspection by auditors from regulatory authorities, as required by ICH GCP. I will assure that the investigational product(s) supplied by the sponsor will be used only as described in the above named protocol.

To be signed by Principal Investigator and Sub- or Co-Investigators (as appropriate).

Please print names and dates next to the corresponding signatures

Signature	Name	Date (dd-mmm-yyyy)

Appendix B
Contra-indications and warnings/precautions of study medication

Amisulpride – contraindications
- ✓ hypersensitivity to (in)active ingredients
- ✓ prolactin-dependent tumors (e.g. breast cancer)
- ✓ phaeochromocytoma (neuroendocrine tumor of the medulla of the andrenal glands
- ✓ use of medication that can induce torsades de pointes:
  - class Ia antiarrhythmic agents (e.g. quinidine, procainamide)
  - use of class III antiarrhythmic agents (e.g. sotalol, amiodarone)
  - other medications such as methadone, bepridil, cisapride

Amisulpride – warnings/precautions
- ✓ Neuroleptic Malignant Syndrome
- ✓ Hyperglycaemia – check & manage
- ✓ Decrease dose in case of renal insufficiency
- ✓ Lowering of seizure threshold – monitor patients with history
- ✓ Caution in combination with alcohol
- ✓ Patients with a history or a family history of breast cancer should be closely monitored during amisulpride therapy.

Need for ECG monitoring during study is assessed at individual basis. <u>The dose of amisulpride needs to be reduced if the QT-interval is prolonged, and discontinued if QTc-interval is > 500ms.</u>

<u>Acute withdrawal symptoms are rare but include:</u>
Nausea, vomiting, insomnia, recurrence of psychotic symptoms and EPS.

Olanzapine – contraindications
- ✓ hypersensitivity to (in)active ingredients
- ✓ known risk of narrow-angle glaucoma

Olanzapine – warnings/precautions
- ✓ Neuroleptic Malignant Syndrome
- ✓ Hyperglycaemia – check & manage
- ✓ Lipid alterations – check & manage
- ✓ Decrease dose in case of hepatic insufficiency
- ✓ Lowering of seizure threshold – monitor patients with history
- ✓ Caution in combination with alcohol

<u>Acute withdrawal symptoms are rare but include:</u>
Sweating, insomnia, tremor, anxiety, nausea & vomiting.

Clozapine – contraindications
- ✓ hypersensitivity to (in)active ingredients
- ✓ patients not able to have blood frequently drawn
- ✓ history of agranulocytose (either due to clozapine or not)
- ✓ bone marrow dysfunction
- ✓ uncontrolled epilepsy
- ✓ alcohol and drugs
- ✓ circulatoire collaps or CNS depression
- ✓ serious renal or cardiac impairment
- ✓ specific hepatic dysfunctions
- ✓ paralytical ileus
- ✓ use of medication associated with agranulocytose

Clozapine – warnings/precautions

- ✓ agranulocytosis (stop medication if this occurs)*
- ✓ myocarditis / cardiopathy (stop medication if this occurs)
- ✓ orthostatic hypertension may occur
- ✓ QT interval prologation may occur
- ✓ dose-related seizures may occur– monitor patients with history
- ✓ monitor patient with hepatic dysfunctions
- ✓ monitor existent prostate enlargements & narrow-angle glaucoma
- ✓ monitor fever
- ✓ hyperglycaemia – check & manage

*** Check SPC for explicit leucocyte blood counts & treatment instructions**

<u>Acute withdrawal symptoms include:</u>
Insomnia, sweating, headache, nausea, vomiting & diarrhea.

Beware of the following aspects:

1. In line with general practice, test for leucocyte count each week according to local guidelines.
2. Warn patient NOT to stop smoking SUDDENLY without discussion this with physician.
3. Instruct patient to report any flu-like symptoms, may be a sign of agranulocytosis.

Appendix C
Publication policy

1. Introduction

This appendix describes the policy for data analysis and publications for Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE). This plan was derived from policies and practices that were utilised in other multicenter academic studies and is in accordance with the principles and standards of scientific research and scholarship within the fields of biomedical research and scientific journalism. The goals of the policy are:
1) to provide for the timely, scholarly and comprehensive reporting of the data in the scientific literature;
2) to provide for the assignment of authorship and data analytic opportunities to study investigators in a manner that is equitable and supports career development;
3) to ensure that the analysis and reporting of data are consistent with regulatory agency requirements.

2. Administrative Structure

The data analysis and publication strategy will be determined by the Executive Board comprised by all study collaborators and investigators. All study publications must be submitted for review to the Executive Board. No treatment group information will be made available until after study completion.

3. Data Analyses

Data analyses will be conducted in a timely fashion in a manner that ensures the study's scientific integrity. The final analysis will be done after all patients have completed the follow up visits, queries have been solved and the database is locked. No interim analysis is planned. Data will be analysed first for the comprehensive sample. After the first publication of the comprehensive sample has been published, reports of individual sites' data may be developed. Data from the individual sites may be used in the development of grant applications at any time provided it doesn't compromise the study's integrity.

4. Levels of Analysis

It is expected that there will be at least four levels of analyses and reports from the study. The first contains analyses specified in the primary hypotheses and variables of the protocol. The second consists of those specified in the secondary hypotheses and variables of the protocol. In the third there are analyses of variables or sub-variables that are not specified in the primary and secondary hypotheses or are directly derivative of them. The fourth level consists of analyses of individual site(s) data. The primary and secondary analyses are described in the Description of Work, and will be managed by the Work Package leaders. In case conflicts arise, these may be resolved by the Executive Board.

5. Submission and review procedures for tertiary and quaternary analyses

Proposals for data analyses and manuscript development will be submitted to the Executive Board for review. Prof. Kahn will co-ordinate this process. Each proposal will be logged in and distributed to each country co-ordinator. The format for the proposal will be no more than two pages and include 1) Specific Aims; 2) Hypotheses; 3) Background and Rationale; 4) Variables to be analysed including time period. Preliminarily approved proposals will be assigned for development to the proposing investigator and interested investigators from other sites. Manuscripts will be developed as per the guidelines below. All documentation will be kept by the central study team.

6. Determination of Authorship

The number and composition of co-authors will be defined based on prevailing standards of scientific scholarship.

The following criteria will be utilised in a system for allocation of authorship.

- Expertise
- Source of idea for analysis or report
- Role in the study's development and implementation
- Role in data analyses
- Role in writing the article
- Study recruitment

7. Conditions and Limitations on Authorship

The following conditions and limitations on authorship are relevant:

- The first overall study publication will include (at least) the Principal Investigators, Trial Coordinators and country co-ordinators as authors
- Every site will not necessarily get a first author comprehensive study publication.
- Some form of rotation will be developed for authorship on comprehensive study publications.
- The Executive Board will review site-specific proposals for publication.
- A time limit within which lead authorship assignments must be initiated and/or completed will be established (e.g. six months from assignment and availability of data to the production of a first draft of manuscript). After this time has elapsed lead authorship will be reassigned.

To resolve any differences or questions regarding authorship or prioritisation of data analyses the following criteria will be used:

1. Scientific merit of the topic
2. Resource requirements in terms of time and effort of the request
3. Number of prior proposals and requests of the investigator
4. Number of prior first authored papers by the investigator
5. Overall contribution to the study